BEHAVIOURAL RESPONSES TO MANIPULATION OF CENTRAL MONOAMINE SYSTEMS IN THE RAT

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ABSTRACT

In psychiatric illnesses, particularly in the affective disorders, and to a lesser extent in the schizophrenias, there are marked deviations from normal behaviour which have components which may be described, in psychological terms as aberrant, stereotyped, activity and as abnormalities in locomotor and exploratory drives.

A hypothesis that a disturbance in one or more of the dopaminergic, noradrenergic or serotonergic neuronal systems in the brain may play a role in psychiatric illness has engendered much research into the functional roles of these systems in animals and man. The published work has been reviewed particularly that in relation to the behavioural abnormalities which may be induced in lower animals such as the rat and which appear to mimic to some degree the abnormalities in behaviours seen in psychiatric illness in man.

The experimental work presented in this thesis is a further contribution to this investigation using an animal model. Previous reports in the literature had, when considered together, indicated that in animals dopaminergic systems played a major role in the mediation of all three types of behaviour monitored - exploratory, locomotor and stereotyped behaviour, with lesser roles being assigned to noradrenergic and serotonergic systems. Individually, the previous studies tended to depend on visual observation of one, or at most two, of these aspects of behaviour, with exploratory behaviour receiving much less attention than stereotyped or locomotor behaviour.

This thesis reports the use of a specially designed automated "hole-board" apparatus for the automated recording of exploratory, locomotor and stereotyped behaviour in rats. The automated recordings were backed up by visual observation of behaviour through closed-circuit television monitoring.

The behavioural responses to a variety of drugs with varying degrees of selectivity on individual monoamine systems were studied. Amphetamine, which releases all three monoamines from neuronal terminals, at low doses (2 and 4 mg/kg of the DL-sulphate i.p.) led to a stimulation of exploratory and locomotor behaviour as well as sniffing and rearing while a larger dose (8 mg/kg) induced intense stereotyped activity. Haloperidol, a selective dopamine receptor antagonist, virtually abolished both spontaneous and amphetamine-stimulated exploratory, locomotor and stereotyped behaviour in a dose-related manner. Repeated weekly administration of amphetamine led to a potentiation of the response to the drug. Paradoxically, chronic haloperidol pretreatment also led to a potentiation of the response to amphetamine. Phenoxybenzamine (20 mg/kg of the hydrochloride i.p.), an α adrenoceptor blocker reduced amphetamine-induced exploratory and locomotor behaviour but not stereotypy. Methysergide, a 5-HT receptor blocker, led to a moderate potentiation of the stimulation of all three behaviours by amphetamine; this was not statistically significant.

The "tricyclic" antidepressant drugs desmethylimipramine and chlorimipramine caused a reduction in spontaneous activity which was more marked with the former drug. GEA 654, a selective inhibitor of neuronal 5-HT uptake, induced a moderate stimulation of locomotor and hole-dipping behaviour not statistically significant.

These three drugs, as well as SKF-525A, an inhibitor of the hepatic microsomal enzyme systems, all potentiated the behavioural response to amphetamine; this potentiation was in the same rank order as their ability to elevate plasma and brain amphetamine levels.

LRCL 5182, a selective inhibitor of neuronal dopamine uptake, and benztropine, an inhibitor of neuronal dopamine uptake which also has potent anticholinergic activity, both induced a marked stimulation of exploratory, locomotor and stereotyped behaviour.

Selective bilateral destruction of dopaminergic neuronal terminals in the accumbens nuclei with 6-hydroxydopamine reduced spontaneous and amphetamine-induced locomotor and exploratory behaviour and sniffing activity; amphetamine-induced stereotyped behaviour appeared to be potentiated. Similarly induced bilateral destruction of dopaminergic nerve endings in the caudate-putamen reduced spontaneous activity; amphetamine-induced stereotyped behaviour was abolished. Some animals with severe degrees of neostriatal dopamine depletion were completely unresponsive to amphetamine, apart from intense sniffing activity. Bilateral electrolytic lesions of the accumbens nuclei did not lead to any change in spontaneous or amphetamine-induced activity.

Bilateral stereotactically-controlled injections of dopamine (5-50 µg of the hydrochloride salt) into the nucleus accumbens of nialamide-pretreated rats induced a marked stimulation of exploratory and locomotor activity, accompanied by intense sniffing and rearing. Conversely, bilateral injection of dopamine (12.5 - 50 µg of the hydrochloride salt) into the caudate-putamen induced intense stereotyped activity which was dose-related. Both responses were blocked by i.p. haloperidol.

Bilateral injection of noradrenaline (50 µg of the hydrochloride salt) into the accumbens nuclei did not produce any significant behavioural change. The same injection intothe caudate-putamen led to a moderate stimulation of stereotyped activity.

Bilateral injection of 5-HT (50 µg of the bimaleinate salt) into the accumbens nuclei induced a moderate locomotor activity with some hole-dipping activity and sniffing; these behaviours were incoordinated and indecisive. The same injection into the caudate-putamen led to a stimulation of locomotor activity and hole-dipping which was predominantly "stereotyped" in character; on visual observation no other striking abnormalities were noted.

The experimental results have been critically discussed. It was concluded that dopaminergic inputs into the accumbens nuclei exerted a major mediatory influence on exploratory and locomotor behaviours while dopaminergic inputs into the caudate-putamen were responsible for the mediation of stereotyped activities.

The implications of these findings with respect to the behavioural changes in psychotic illness were discussed. On the basis of comparisons between the changes in psychotic illness and the changes in behaviour induced by stereotactic manipulations of the accumbens nuclei and caudate-putamen, it was proposed that dopaminergic influences in the accumbens nuclei probably play a major role in the affective disorders, with probable additional involvement of the caudate-putamen in severe illness. Two animal models of mania were proposed based on the stimulation of exploratory, locomotor and stereotyped behaviour in animals by amphetamine and the stimulation of locomotor and exploratory activity by application of dopamine into the accumbens nuclei.

There were less clear-cut resemblances between the effects of manipulation of the three monoamine systems on behaviour in animals and the behavioural changes seen in the schizophrenias. It was suggested that serotonergic influences may be involved in the behavioural changes seen in schizophrenia.

Statement in Terms of Ph.D. Regulation 2.4.15

All work described in this thesis was performed by the author with the following exception:

Computer analysis of behavioural records from the hole-board apparatus was performed by Dr. Graham Hill.

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ABBREVIATIONS

CMI	- Chlorimipramine
DA	- Dopamine, dopaminergic
D-	- Dextro isomer
DL-	- Racemic isomer
L-DOPA	- L-Dihydroxyphenylalanine
DMI	- Desmethylimipramine
5-HIAA	- 5-Hydroxyindoleacetic acid
HMPG	- 4-Hydroxy,3-Methoxy,phenethylene glycol
5-HT	- 5-Hydroxytryptamine, 5-Hydroxytryptaminergic
HVA	- Homovanillic acid
i.p.	- intraperitoneal
LSD	- Lysergic acid diethylamide
5-MEODMT	- 5-Methoxy,-N,N,-dimethyltryptamine
NA	- Noradrenaline, noradrenergic
5-OHTP	- 5-Hydroxytryptophan
S.E.M.	- Standard Error of the Mean

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SUMMARY

1. The experimental work reported in this thesis represents a contribution to the continuing study, using animal models, of the possible roles of dopaminergic, noradrenergic and serotonergic neuronal systems of the central nervous system in the mediation of exploratory, locomotor and stereotyped behaviours. The rat was the species used in the study.

2. A review of the previous work in this field is presented together with a discussion of the relevance of such investigation of behavioural changes induced in animal models to the elucidation of the cause of deviations from normal behaviour in psychotic illness in which components of aberrant, stereotyped activity and abnormal exploratory and locomotor drives can be discerned.

3. The use of a specially designed "hole-board" apparatus located in a constant environment allowed simultaneous and continuous measurement of all three types of behaviours, thus improving to some extent on the subjective visual assessment employed in most previous work of only one, or at the most two, of the aspects of the behavioural response. The exploratory and stereotyped activity monitored in the 'hole-board' apparatus was characterised by head dipping into the holes in the floor of the enclosure, the frequency and pattern of movement in relation to the various holes serving to assess the intensity of the two types of activity. A closed circuit

television circuit permitted observation without disturbance to the animal; by this means features of the behavioural pattern which were not monitored automatically could be noted.

4. The attempt to assess the roles of the monoamine neuronal systems was made by analysing the incidence and variation of the behavioural responses after pharmacological or physical manipulation of the systems by methods of varying degrees of selectivity for each system. Such manipulation included systemic (i.p.) administration of selected drugs and chemical and electrolytic lesioning of, and the application under stereotactic control of each of the monoamines to, the caudate-putamen nuclei and to the accumbens nuclei, areas which earlier work had indicated to be of major importance to the behavioural responses.

5. The behavioural responses to various drugs which cause, with varying degrees of selectivity, activation of central monoamine receptors, were studied after i.p. administration.

Amphetamine, a releaser of monoamine neurotransmitters, induced in low doses (2 and 4 mg DL-sulphate/kg) a stimulation of exploratory and locomotor activities which included sniffing and rearing as well as the measured hole-dipping and horizontal locomotor movements. With a higher dose marked stereotyped hole-dipping activity eventually appeared with reciprocal depression of the initially stimulated exploratory and locomotor behaviour.

Haloperidol, a selective dopamine receptor antagonist, reduced both spontaneous and all amphetamine-induced behaviours in a dose-related manner.

Repeated weekly administration of amphetamine resulted in potentiation of the responses to this drug. Paradoxically, chronic haloperidol treatment also produced an increase in the sensitivity to amphetamine.

Phenoxybenzamine (20 mg hydrochloride/kg), a monoamine receptor antagonist showing selectivity towards α - adrenoceptors, markedly reduced the exploratory and locomotor response to amphetamine (4 mg DL-sulphate/kg) given subsequently.

The behavioural responses to this dose of amphetamine appeared somewhat potentiated by pretreatment with methysergide (2 mg hydrogen maleinate/kg), a serotonin (5-hydroxytryptamine, 5-HT) receptor antagonist; the potentiations were not statistically significant.

Apomorphine, reputedly a selective dopamine (DA) receptor agonist, stimulated (on visual observation) exploratory (0.75 mg hydrochloride/kg) and stereotyped (higher doses) behaviours both of which had a large component seemingly directed towards olfactory ('sniffing') and gustatory ('gnawing and biting') stimulation. Consequently the intensities of the exploratory and stereotyped responses to this drug were not adequately quantified by the hole-board technique.

5-Methoxy,-N,N,-dimethyltryptamine, a putative 5-hydroxytryptamine receptor agonist, induced with all doses in the tested range (2.5 - 10 mg/kg) a bizarre behavioural syndrome of incoordinated hyperactivity, tremor, sniffing,

head-nodding, hyperextension of the body, and abduction and rigidity of the tail.

The two 'tricyclic' antidepressant drugs desmethylimipramine and chlorimipramine, inhibitors of neuronal NA and 5-HT reuptake, caused behavioural sedation; this was more marked with desmethylimipramine.

A selective inhibitor of neuronal 5-HT uptake GEA 654, caused a moderate stimulation of locomotion and hole-dipping activity; these changes were not statistically significant.

LRCL 5182, a selective inhibitor of neuronal DA uptake, at the lower dose employed (10 mg/kg) led to a stimulation of exploratory and locomotor activity; a dose of 20 mg/kg led to a further increase in locomotor activity as well as intense stereotyped behaviour.

Benztropine, a drug which combines anticholinergic properties with potent actions in inhibiting neuronal DA uptake, led to a stimulation of exploratory and stereotyped behaviour and, particularly at the lower dose (2.5 mg/kg of the mesylate salt), of locomotor activity.

The tricyclic antidepressants, desmethylimipramine and chlorimipramine and the selective 5-HT uptake inhibitor GEA 654 markedly potentiated the behavioural response to amphetamine (4 mg DL-sulphate/kg) as did the inhibitor of 'liver microsomal enzyme' activity, SKF-525A. The degree of potentiation was quantitatively associated with higher concentrations of amphetamine in brain making it improbable that actions on neuronal uptake mechanisms played a prominent role in this potentiation.

7. The effects on behaviour of localised manipulations of the monoaminergic systems in selected brain areas were studied.

a) Selective destruction of dopaminergic nerve terminals in the accumbens nuclei by bilateral stereotactically controlled intracerebral administration of 6-hydroxydopamine reduced spontaneous and amphetamine-induced locomotor and exploratory behaviour including sniffing; stereotyped behaviour appeared to be potentiated.

Similarly induced bilateral destruction of dopaminergic nerve terminals in the caudate-putamen nuclei reduced spontaneous activity. The production of stereotyped behaviour by amphetamine was prevented but the stimulatory actions of this drug on locomotor and exploratory behaviour were reduced to a lesser degree. Some animals with severe neostriatal dopamine depletion were completely unresponsive to amphetamine, apart from intense sniffing activity.

Bilateral electrolytic lesions of the accumbens nuclei had no effect on spontaneous or amphetamine-induced activity.

b) The behavioural responses following stereotactically controlled intracerebral injections of dopamine, 5-hydroxytryptamine and noradrenaline in nialamide-pretreated rats were studied.

Bilateral injections of dopamine (5-50 µg of the hydrochloride salt) into the nucleus accumbens of nialamide-pretreated rats induced a marked stimulation of exploratory and locomotor activity, accompanied by intense sniffing and rearing; stereotyped activity was much less affected.

In contrast, bilateral injection of dopamine (12.5 - 50 µg of the hydrochloride salt) into the caudate-putamen induced intense stereotyped activity which was dose-related; exploratory and locomotor activity were much less affected. Haloperidol (i.p.) blocked both responses.

Bilateral injection of noradrenaline (50 µg of the hydrochloride salt) into the accumbens nuclei did not produce any significant behavioural change. The same injection into the caudate-putamen led to a moderate stimulation of stereotyped activity.

Bilateral injection of 5-HT (50 µg of the bimaleinate salt) into the accumbens nuclei induced a moderate locomotor activity with some hole-dipping activity and sniffing; these behaviours were uncoordinated and indecisive. The same injection into the caudate-putamen led to a slight stimulation of locomotor activity and hole-dipping which was predominantly "stereotyped" in character; on visual observation no other striking abnormalities were noted.

8. The experimental results have been critically discussed and the following conclusions have been drawn:

Dopaminergic systems play a major role in the regulation of all three forms of behaviour studied - exploratory, locomotor and stereotyped. The noradrenergic and serotonergic systems may also play a minor, complementary role. Furthermore, the different behaviours appear to be regulated from different dopaminergically-innervated areas. The behavioural components of exploration (as evidenced by "exploratory" hole-dipping, locomotion, sniffing and rearing) are mediated through

the accumbens nuclei and possibly also the olfactory tubercles. Stereotyped behaviour (as evidenced by "stereotyped" hole-dipping and "non-dipping stereotyped behaviour" consisting of other types of repetitive head movements as well as intense gnawing and biting) is mediated through the caudate-putamen. It also seems likely that some degree of dopaminergic activity in the caudate-putamen is necessary for all forms of behaviour to be able to occur, including those mediated primarily from other areas.

In spite of the fact that the two groups of activities (exploratory and locomotor activities on the one hand and stereotyped activities on the other) appear to be mediated from different anatomical loci, there still appears to be a close relationship between them in intact animals, as evidenced in the selective effects of different doses of dopamine agonist drugs on them. (Observation of these relationships was facilitated by the hole-board technique employed, which allows simultaneous quantitative evaluation of all these behaviours). The nature of this relationship has been discussed.

Since many of the behavioural changes observed in the affective disorders in man appear to be mediated through dopaminergic systems in the rat, it seems likely that disturbances of dopaminergic systems play a major role in the manifestation of these disorders. Furthermore, it is proposed that disturbances in the accumbens nuclei may play a prominent role, with involvement of the nigro-striatal system probably also featuring in the more severe forms of the illness.

Two animal models of mania are proposed (a) the behavioural effects of increasing dosage with amphetamine and (b) the response to dopamine injection into the accumbens nuclei.

Less evidence could be found from these animal studies of a role for dopaminergic systems in schizophrenia. It was speculated that 5-hydroxytryptaminergic systems might be involved in the behavioural changes observed and the similarities between the behavioural effects of a systemically administered serotonergic agonist and of 5-hydroxytryptamine injected into the accumbens nuclei and some of the symptomatology of schizophrenia were discussed.

I. INTRODUCTION

The aim of this study was to examine the roles of different monoamine transmitter systems in the mediation of exploratory, stereotyped and locomotor behaviours. The three monoamine systems concerned are those in which transmitter function is subserved by dopamine (DA), noradrenaline (NA) and 5-hydroxytryptamine (5-HT). The work represents an extension of a part-time project reported in an M.Phil. Thesis (Makanjuola, 1976).

Two main lines of reasoning provide the rationale for this study. Firstly, since there is a large body of evidence linking functional psychotic illness with disturbances of monoamine systems, it should assist our understanding of these illnesses to study the functions, particularly the behaviours, which are influenced by these systems, and the specific roles that these monoamine systems play in mediating the behaviours. Exploratory, locomotor and stereotyped behaviours are some of the activities known to be influenced by monoamine pathways. Secondly, changes in all three behaviours have been observed in functional psychotic illness. Parallel studies of the behaviours in man (both in health and psychosis) and animals should therefore assist our understanding of the roles of monoamine systems in the behavioural changes of psychotic illness and possibly the aetiology of the illness itself. These points are discussed in greater detail below.

1. DEFINITIONS

Exploratory Behaviour. The concept of exploratory behaviour is open to some variability in definition, particularly when applied to man, where thinking is taken into consideration in addition to overt activity. Welker's (1962) definition, which is taken as the operational definition in this study, states that exploratory behaviour consists of behaviour motivated towards sensory stimulation, with the emphasis being on novel sources of stimulation. I believe this definition to be valid in relation to behaviour in small animals, in which it is assumed that the majority of behaviour would be manifested externally, which makes internalized thought processes less important.

Stereotyped Behaviour. There is little disagreement about definition here. Stereotypy is defined as repetitive, apparently purposeless patterns of behaviour (Randrup and Munkvad, 1974; Wallach, 1974).

Locomotor Behaviour. This type of behaviour is often confused with exploratory behaviour. It refers to the process by which the animal moves from place to place, and may be motivated by considerations other than exploration.

General Activity. Locomotion has to be further differentiated from general activity. This term refers merely to body movements which may not necessarily be locomotor in nature. Measurements obtained from 'activity' boxes

quantify general activity and do not necessarily accurately measure movement from place to place, yet some authors use results from such apparatus as indicators of the intensity of locomotor or even exploratory activity.

2. CLINICAL RELEVANCE OF EXPLORATORY, STEREOTYPED AND LOCOMOTOR BEHAVIOURS

a. MONOAMINE THEORIES OF FUNCTIONAL PSYCHOSES

Disturbances of monoamine systems have long been implicated in psychiatric illness, in particular the two major forms of functional psychosis, the affective disorders and schizophrenia.

The main body of evidence for the assumption that disturbances of monoamine systems are involved in the affective disorders lies in the fact that many of the drugs useful in the treatment of these disorders appear to alter preferentially activity in these systems. Antidepressant drugs increase the amounts of monoamine transmitters available to stimulate post-synaptic receptors, either by monoamine oxidase inhibition (Zeller et al.1962; Spencer, 1977) or by the inhibition of the neuronal re-uptake of released monoamines (Glowinski and Axelrod, 1966; Iversen, 1975; Schacht et al. 1977) or by both mechanisms (Iversen, 1975; Roth, 1978). Certain monoamine oxidase inhibitors e.g. tranylcypromine, may also release monoamines (Marley and Stephenson, 1972).

Depressive illness may also be alleviated by treatment with L-tryptophan, the amino-acid precursor of 5-HT, particularly when combined with monoamine oxidase inhibition (Coppen, 1967; Prange et al. 1974).

Treatment with L-dihydroxyphenylalanine (L-DOPA) the immediate precursor of DA has been less successful (Goodwin and Sack, 1974). Lithium salts have also been used successfully in the treatment and prophylaxis of affective disorders. The mode of action of the lithium ion is still unclear; it has been suggested that it may produce effects on monoamine systems by alterations in cellular ion transport dependent on adenosyl triphosphatase activity (Glen and Reading, 1974). Electroconvulsive therapy may produce improvement in depressive illness by increasing neuronal receptor sensitivity (Evans, et al. 1974).

A variety of drugs which decrease activity in monoamine systems are capable of inducing depressive symptoms. The best known example is reserpine (Achor et al. 1955; Muller et al. 1955). This drug causes a depletion of all three monoamines from their neurones (Holzbauer and Vogt, 1956; Pletscher et al. 1956; Häggendal and Lindqvist, 1964). The psychological impact of chronic illness may make a substantial contribution to depressive symptomatology associated with antihypertensive mediation, including reserpine (Bant, 1978). Tetrabenazine, which has similar actions to reserpine (Lingjaerde, 1963) also causes depressive symptoms (Lingjaerde, 1963). Parachlorophenylalanine, which depletes 5-HT neurones of their transmitter by tryptophan hydroxylase inhibition (Koe and Weissman, 1966) also causes depressive symptoms (Engelman et al. 1967). Neuroleptic drugs used in the treatment of mania block monoamine, especially dopaminergic, receptors (Anden et al. 1970a; Carlsson, 1974, 1978;

Seeman et al. 1976). Neuroleptic drugs do not however consistently cause depression, possibly because of their specific action on dopaminergic neuronal systems. Both triyclic antidepressant drugs and monoamine oxidase inhibitors may occasionally precipitate manic episodes (Davis and Janowsky, 1974).

This evidence regarding drug effects in the therapy and in the induction of affective disorders would at first appear overwhelming. However, it must be stressed that the fact that manipulation of monoamine systems by drugs leads to amelioration of symptoms in the disorder or to the induction of symptoms associated with the disorder does not necessarily imply that the primary disorder lies within those systems. Whatever area or areas of the brain is primarily responsible for the affective disorder, it may be subject to a variety of modifying inputs, including monoaminergic inputs. Alternatively, changes in monoamine systems may be the result of inputs into them from another system or brain area more fundamentally involved in the affective disorder.

Unfortunately attempts to demonstrate changes in monoamine systems in patients with affective disorder have produced inconsistent results which require increasingly complicated formulations to explain. Most such studies have involved biochemical examination of cerebrospinal fluid (CSF) obtained, in most studies, from the lumbar region. Decreases in all three major metabolites of the amines have been reported in depressive illness. This applies most consistently to the 5-HT metabolite, 5-hydroxy-

indole acetic acid (5-HIAA) (van Praag et al. 1972; Coppen et al. 1972; MRC Brain Metabolism Unit, 1972) but decreases in the DA metabolite, homovanillic acid (HVA) (Roos et al. 1969; Papeschi and McClure, 1971; MRC Brain Metabolism Unit, 1972) and the NA metabolite 4-hydroxy-3-methoxy, phenethylene glycol (HMPG) (Post et al. 1973) have also been reported. Changes in mania are less striking, although rises in HMPG have been described (Wilk et al. 1972; Pullar, 1973).

The interpretation of these observations is made difficult by the fact that metabolite levels may not return to normal on recovery (Coppen et al. 1972; MRC Brain Metabolism Unit, 1972). Furthermore, the changes in metabolite concentration were not universally observed. It was to accommodate these disparate findings that the concept of changes in post-synaptic receptor sensitivity was introduced (MRC Brain Metabolism Unit, 1972).

There are major basic problems in interpreting results from CSF studies. First, changes in monoamine turnover in specific areas may be masked by changes elsewhere. Changes in the concentrations of CSF metabolites cannot even be guaranteed to reflect changes in brain monoamine activity. While in lumbar CSF the HVA probably derives from brain DA metabolism, there is considerable doubt as to what proportion of lumbar CSF 5-HIAA comes from spinal cord or brain and most of the HMPG appears to come from the spinal cord (Garelis et al. 1974).

An alternative approach is the study of monoamine and metabolite content of human brain. Brain biopsy may not

be practicable for ethical reasons. Post-mortem studies are bedevilled by the problems of variable time between death and delivery of the post-mortem sample and sometimes of specimen storage. Furthermore the mode of death may itself have a profound effect on such estimations. Reduced 5-HT and 5-HIAA levels in brains of depressed people who committed suicide have been found (Shaw et al. 1967; Bourne et al. 1968). In another study of depressed persons who committed suicide (Pare et al. 1969) DA, NA and 5-HIAA levels were unchanged although there was a slight reduction in 5-HT levels.

On the basis of the above evidence, and in spite of the deficiencies, disturbances of monoamine systems have been embodied in various theories of affective disorder. These theories imply that in depressive illness there is a reduction in effective activity of catecholamine systems (Schildkraut, 1965) or 5-HT systems (Coppen, 1967) as a result either of a decrease in monoamine neuronal activity itself or a decrease in post-synaptic monoamine receptor sensitivity (MRC Brain Metabolism Unit, 1972). Mania is considered to be associated with overactivity of the systems arising in a manner converse to those operating in depression. Prange et al. (1974) implicated all three monoamine systems in affective disorder. According to their theory central 5-HT underactivity predisposes to affective disorder whereas episodes of illness manifest with additional changes in catecholamine systems. The changes in 5-HT metabolism may represent the constitutional predisposition to the illness (Schildkraut, 1973).

Similar problems apply to examination of the hypotheses relating schizophrenia to abnormal function in monoamine systems. Currently, the most plausible contender is the "dopaminergic theory" of schizophrenia (Snyder et al. 1974; Carlsson, 1978) which states that schizophrenia involves overactivity of dopaminergic systems resulting either from increased neuronal activity or from increased DA receptor sensitivity. The main body of evidence for this theory lies in the fact that drugs effective in alleviating the symptoms of schizophrenia are potent DA receptor blockers, and it is this property that is essential for their clinical effectiveness (Andén et al. 1970a; Carlsson, 1974, 1978; Seeman et al. 1976).

Amphetamine and related sympathomimetic substances induce in man an illness very similar to paranoid schizophrenia (Connell, 1958; Angrist et al. 1974). Furthermore these drugs are capable of exacerbating the symptoms of schizophrenia (Davis and Janowsky, 1973). These drugs increase activity in monoamine systems, mainly by inducing transmitter release from neurone terminals (see page 24). Other drugs which stimulate dopaminergic and other monoamine systems such as cocaine and L-DOPA can also induce or exacerbate schizophrenia-like illnesses in man (see Snyder et al. 1974). Psychoses and schizophrenic exacerbations induced by amphetamine and its derivatives are alleviated by haloperidol (Angrist et al. 1974) which is a potent antagonist at DA receptors (Andén et al. 1970a; Seeman et al. 1976).

Recently, evidence has been accruing that neuroleptic drugs alleviate the symptoms of schizophrenia through their actions on mesolimbic DA systems whereas their ability to induce "extrapyramidal" symptoms is related to their actions on the nigro-striatal DA system (Andén and Stock, 1974; Crow & Gillbe,1975). Furthermore, the differential action of some neuroleptic drugs on mesolimbic or nigro-striatal DA turnover is related to the relative amount of antimuscarinic activity possessed by the drugs (Miller and Hiley, 1974). For example, clozapine and thioridazine which in contrast to haloperidol and chlorpromazine have relatively high antimuscarinic activity and tend to be associated with a relatively low incidence of extrapyramidal side effects, tend to be much more potent in their effects on DA turnover in the mesolimbic DA system. It has been demonstrated that whereas drug-induced alterations in dopaminergic activity leads to changes in cholinergic function in the nigro-striatal system, no such changes occur in the mesolimbic DA system (Ladinsky et al. 1978). It may be that the differential effects of neuroleptic drugs on mesolimbic as opposed to nigro-striatal DA turnover is related to this apparent resistance in the mesolimbic system towards dopaminergically induced changes in cholinergic function.

More direct attempts to demonstrate changes in dopaminergic systems in the brains of schizophrenic patients have not yielded much evidence in support of the dopamine hypothesis of schizophrenia. There is some speculation that disorders in the limbic system, most

areas of which have a very high level of dopaminergic innervation (Ungerstedt, 1971a; Lindvall and Bjorklund, 1974; Jacobowitz and Palkovits, 1974) are involved in schizophrenia (Torrey and Peterson, 1974). Recently it was demonstrated that in brains of schizophrenics obtained at post-mortem there was a relatively selective increase in DA content and decreases in glutamic acid decarboxylase and choline acetyltransferase activity in the nucleus accumbens (Bird et al. 1977). However, these changes could have been the result of long-term neuroleptic medication.

While the theories relating monoamine function to psychotic illness are open to much criticism, no other satisfactory alternative has been put forward, and the evidence in favour cannot be ignored. It should still be a useful approach to work under the assumption that central monoamine function is important. If we accept that monoamine function may be important in these illnesses, then one way in which our understanding of these illnesses may be improved is to study the functions, in particular the behaviours, that these systems are concerned with. This concept has stimulated an enormous amount of research, and we now know of a whole host of behaviours influenced by these systems in animals. It follows from here that we should then look for changes in these behaviours in sick people. Once we have an idea as to which of the behaviours is altered in illness, we can go back to our animal models and ask such specific questions as: which subdivisions of these systems are responsible for those

particular behaviours?; how can we modify these behaviours?; can we apply this knowledge to diagnosis and treatment of the human animal?

One example of the way in which this dual approach has been of immense value concerns the treatment of schizophrenia with neuroleptic drugs. For a long time drug-induced stereotyped behaviour was regarded as an animal model for acute psychosis (Angrist and Gershon, 1974; Wallach, 1974). There was also speculation that the use of anticholinergic drugs to treat neuroleptic-induced extrapyramidal symptoms might reduce the effectiveness of neuroleptic medication in alleviating schizophrenic symptoms (Singh and Kay, 1975). We now know both these ideas to be fallacious since the nigro-striatal system is now known to play the major role in mediation of drug-induced stereotyped behaviour (this will be discussed in detail in subsequent pages), and Parkinson's disease (Hornykiewicz, 1972). Neuroleptic-induced Parkinsonism appears to be a function of drug effects on the nigro-striatal system whereas these drugs seem to depend for their therapeutic efficacy on their effects in the mesolimbic dopaminergic system (see page 8). Anti-cholinergic drugs may of course also antagonise neuroleptic drug effects even in the mesolimbic system through their ability to inhibit DA uptake (Coyle and Snyder, 1969).

b. <u>EXPLORATORY, STEREOTYPED AND LOCOMOTOR BEHAVIOUR IN PSYCHOTIC ILLNESS</u>

As will be discussed in detail later, there is substantial evidence that in animals monoamine systems,

particularly the dopaminergic systems, are involved in the mediation of all three behaviours under consideration. It follows from the comments in the previous section that if changes can be found in these behaviours in patients with psychotic illness, this might provide further evidence in support of the monoamine theories of psychotic illness. A fuller understanding of the mediation of these behaviours by monoamine systems in animals and of how the behaviours can be modified should help our understanding of the disease process as well as assisting in the development of effective therapy. For example, if it were found that behavioural changes in one form of psychosis were all mediated by one particular system or subsystem this then would be an indication that that particular subsystem was involved in behavioural changes accompanying the disease. Attention could then be directed towards finding ways of manipulating that particular subsystem appropriately and specifically. This may now be the case in schizophrenia, where efforts might now be directed towards finding drugs with specific effects on mesolimbic DA function.

In fact quite obvious and often gross changes in exploratory and locomotor activity occur in functional psychosis and stereotyped behaviours can also be seen. These behavioural changes are well documented in the classical psychiatric literature (e.g. Kraepelin, 1921; Bleuler, 1950) as well as more recently (MRC Brain Metabolism Unit, 1972). The changes are most obvious in the affective disorders. In retarded depression, the

patient becomes increasingly immobile both in thought and action, and his capacity and motivation for exploratory activity and thought appear greatly decreased. When questioned it is clear that the patient's thoughts revolve slowly round a limited number of topics. However, in some patients, although they appear retarded in activity, their thoughts are reported as going faster than normal, but again these thoughts revolve around a limited number of topics and it is difficult to initiate or sustain other areas of thought. Such thinking can be regarded as stereotyped. In agitated depression exploration is again at a minimum but the patient is hyperactive and one observes intense stereotypy in activity and thought.

In the less severe forms of mania patients are hyperactive and appear to indulge in a high level of exploratory activity which manifests as a restless passage from room to room, object to object, venture to venture and topic to topic. The classical 'flight of ideas' of mania refers to the passage of the subject's thoughts from one idea to the next in rapid succession - a high level of exploratory thinking. In more severe cases exploratory behaviour may be replaced by intense repetitive activity and thought which appears increasingly aimless i.e. stereotypy. In some cases these repetitive actions and thoughts become so intense that it is difficult to distract the patient from them except momentarily. There is an analogy here between this situation and that of a rodent stimulated by drugs into intense stereotyped behaviour - the animal can only be momentarily distracted

from stereotyped behaviour by a relatively intense external stimulation e.g. a loud noise.

A variety of stereotyped behaviours can be observed in schizophrenia, involving both speech and action. Most obvious are the actions and posturings of catatonic schizophrenia. In excited schizophrenic patients much behaviour is repetitive and apparently purposeless.

It is difficult to interpret schizophrenic symptoms in terms of changes in exploratory activity and thought. It could be that the alterations in behaviour do not result simply from quantitative changes in the thought process but rather from a qualitative disorganisation of the thought process. Paranoid ideation in schizophrenia involves an inability of the patient to consider other interpretations of incoming stimuli as alternatives to the delusional interpretation. Changes in motor activity are evident at the two extremes of catatonic schizophrenia - stupor and excitement.

It is well-known that in amphetamine addicts, and particularly in amphetamine psychosis, stereotyped facio-buccal and upper limb movements are commonly seen, as well as more complex stereotyped activities (Ashcroft et al. 1965; Ellinwood, 1967).

The above clinical observations of changes in these behaviours in psychotic illness are based on subjective, often anecdotal, observations. It would be helpful if they could be examined quantitatively and in a more objective way. Unfortunately there are great difficulties here. In animals and children it is relatively easy to

devise measures of these behaviours, but in adults there are major problems. First, adult humans internalize much of their behaviour i.e. much of it involves thought, which is not readily accessible to external assessment. Secondly even their overt behaviour is under a variable, often quite major, degree of constraint from cultural and social influences. Recently a collection of tests has been devised to study these behaviours and applied to the study of changes in these behaviours in affective disorder (Makanjuola and Blackburn, in preparation). In general the findings fitted with the descriptions of changes in these behaviours described above, although certain deficiencies were apparent in the procedure.

3. MONOAMINE PATHWAYS IN THE RAT BRAIN

Most of the work to demonstrate the diffuse innervation of different brain areas by monoamine systems has been carried out in the rat. The work of mapping out the pathways began following the introduction of the Falck-Hillarp formaldehyde fluorescence technique (Carlsson et al. 1962). Progress was facilitated by the introduction of the neurotoxic dihydroxytryptamines 5, 6- and 5, 7-dihydroxytryptamine for the study of 5-HT pathways (Fuxe and Jonsson, 1974) and the glyoxylic acid technique for the demonstration of DA and NA neurons (Lindvall and Bjorklund, 1974). Biochemical, autoradiographic and other neuronal labelling techniques have also assisted in the tracing of these pathways.

Knowledge of the distribution of the monoamine pathways is now extensive and has been thoroughly

reviewed (Ungerstedt, 1971a; Fuxe and Jonsson, 1974; Lindvall and Bjorklund, 1974). The following brief description cannot do justice to the many observations that have been documented. Emphasis is laid on those pathways that are particularly relevant to the present study. The cell group nomenclature used is that of Dahlstrom and Fuxe (1965).

a. DOPAMINERGIC PATHWAYS. There are three main dopaminergic pathways in the brain: (Fig. 1)

(i) The nigro-striatal pathway arises mainly from cell bodies in the zona compacta of the substantia nigra (cell group A9), its rostromedial extension into the ventral tegmentum and the more caudal A8 group. The fibres pass rostro-medially to form a distinct nerve bundle, the nigro-striatal bundle, which ascends in the postero lateral aspect of the medial forebrain bundle and passes rostrally to supply mainly the caudate-putamen. Some fibres also innervate the nucleus interstitalis stria terminalis and anterior limbic cortex.

(ii) The mesolimbic DA system. Fibres of this system arise mainly from cell bodies of the A10 cell group situated dorsal to the interpeduncular nucleus. The fibres ascend in a large bundle along the medial forebrain bundle, where they lie in a ventro-medial position to the nigro-striatal bundle from which there is no real demarcation in this position. The pathway as it ascends divides into various branches which supply mainly areas of the so-called limbic

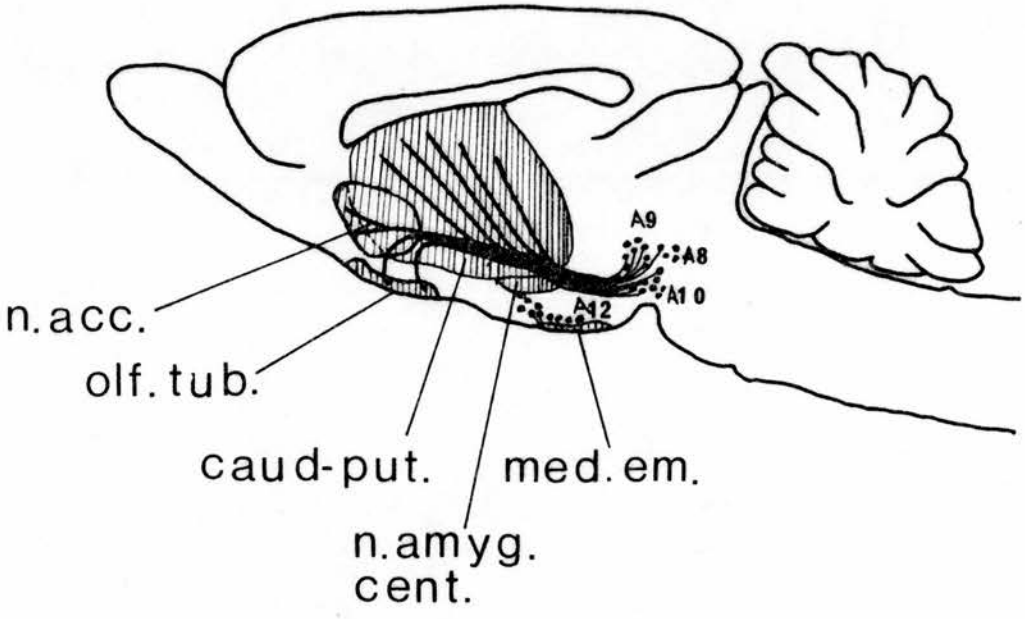


FIG. 1: Dopamine pathways in the rat brain. The nigro-striatal, mesolimbic and tubero-infundibular pathways are depicted. It should be noted that the nigro-striatal and mesolimbic systems cannot easily be distinguished anatomically during most of their course.

n.acc - nucleus accumbens
olf.tub. - olfactory tubercles
caud-put. - caudate-putamen
n.amyg.cent.- central nucleus of the amygdala
med.em. - median eminence.

(After Ungerstedt, 1971a).

system, including the amygdala, piriform, frontal and anterior limbic cortex, septum, olfactory tubercles, olfactory nuclei and accumbens nuclei. The neostriatum also receives some innervation from this system.

(iii) The tubero-infundibular system consists of a system of short dopaminergic neurons within the hypothalamus which are assumed to be concerned mainly with endocrine function.

b. NORADRENERGIC PATHWAYS (Fig. 2)

A dorsal NA pathway arises mainly from cell bodies in the locus coeruleus (A6). It forms a distinct bundle as it ascends rostrally in the medial forebrain bundle. The system supplies mainly dorsal diencephalic and telencephalic areas, including the thalamus, hippocampus and neocortex.

A ventral NA pathway arising from cell bodies in pons and medulla (A1-A6) ascends rostrally and supplies mainly ventral forebrain areas, including the hypothalamus, thalamus, various mesolimbic areas and the neostriatum.

The dorsal and ventral periventricular systems are distributed diffusely along the periventricular and periaqueductal grey matter from the medulla as far as the rostral diencephalon. The two systems receive fibres from medullary and pontine NA cell groups as well as cell bodies distributed along the pathways themselves. The pathways project mainly to thalamic, hypothalamic and mesolimbic areas.

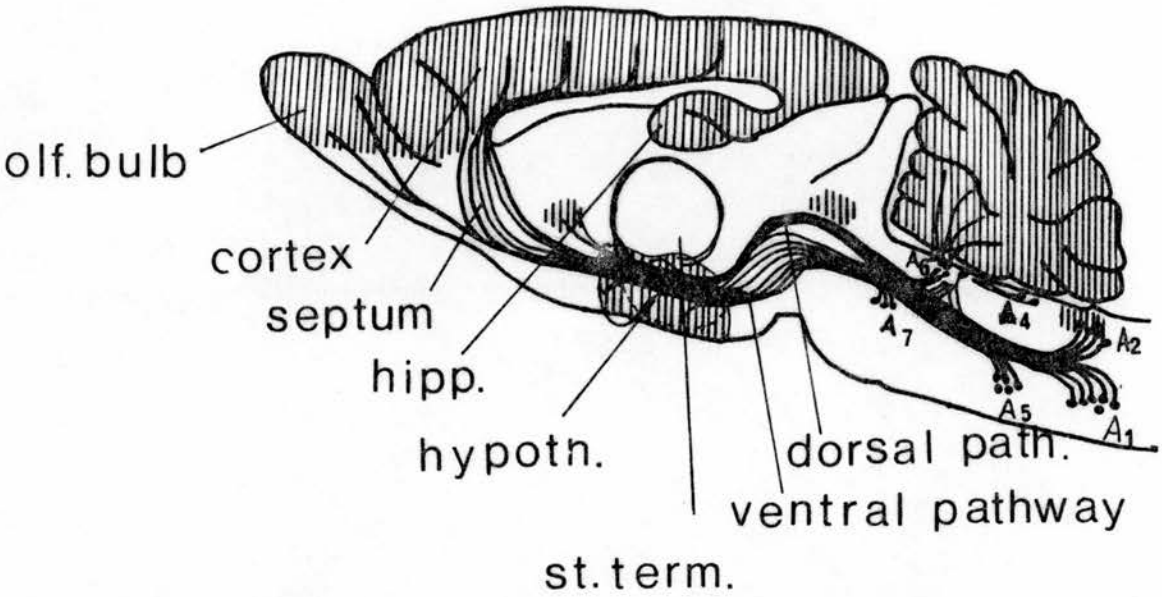


FIG. 2: Ascending noradrenergic pathways in the rat brain. The dorsal and ventral periventricular systems are not shown.

olf.bulb - olfactory bulb
hipp. - hypocampus
hypoth. - hypothalamus
st.term. - stria terminals

(After Ungerstedt, 1971a).

c. SERETONERGIC (5-HT) PATHWAYS (Fig. 3)

Three major ascending pathways have been identified (Fuxe and Jonsson, 1974).

(i) A medial ascending subcortical pathway arises from cell bodies in the pontine raphe (B5 and B6) and from the dorsal and median mesencephalic raphe (B7, B8) and supplies mainly the hypothalamus and pre-optic area.

(ii) A lateral ascending cortical pathway arises from the mesencephalic B7, B8 and B9 cell groups. It ascends in the medial forebrain bundle into the cingulum, thence supplying mainly the cortex, and hippocampus.

(iii) A more lateral pathway arising from B7-B9 cell groups ascends on the inner surface of the crus cerebri to innervate extrapyramidal structures, including the neostriatum and globus pallidus.

On the basis of biochemical and histofluorescence changes following lesions of the midbrain raphe nuclei, it appears that these nuclei project to different brain areas. In particular, the dorsal raphe nuclei (B7) appear to innervate the striatum, thalamus, hypothalamus and cerebral cortex whereas the median nuclei (B8) project mainly to the hippocampus, septum, cerebral cortex and hypothalamus (Lorens and Guldberg, 1974; Geyer et al. 1976a; Geyer et al. 1976b; Samanin et al. 1978).

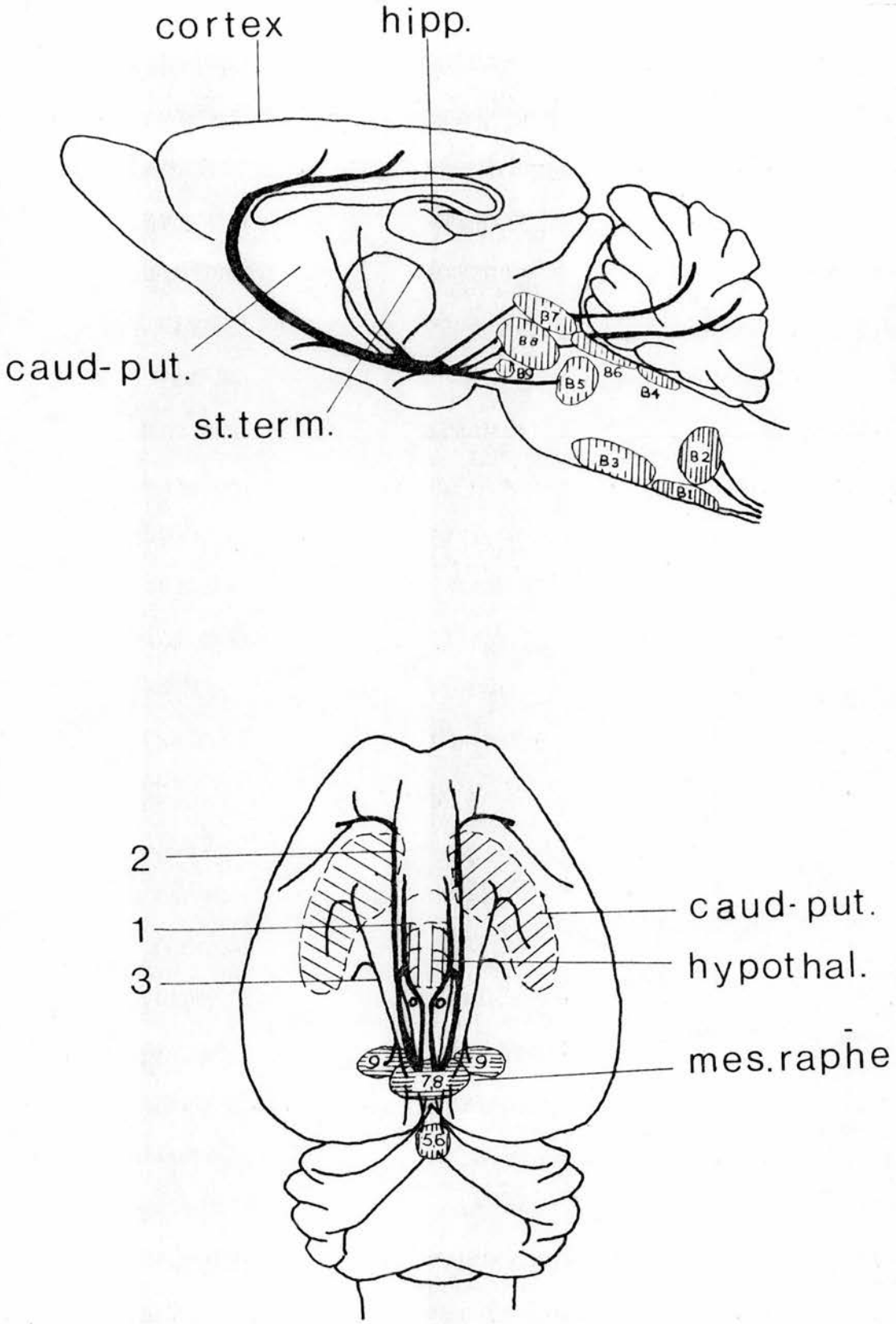


FIG. 3: Ascending 5-hydroxytryptamine pathways in the rat brain. The 3 major pathways (page 18) are best seen in the bottom figure.

1 - medial subcortical pathway supplying mainly hypothalamus and pre-optic area.
2 - lateral ascending cortical pathway, supplying mainly the cortex and hippocampus.
3 - a more lateral pathway supplying mainly extrapyramidal structures.

hipp - hippocampus; caud-put. - caudate-putamen; st.term - stria terminalis; mes.raphe - mesencephalic raphe.

d. MONOAMINE NEURONAL INTERACTIONS

From the above it is evident that many brain areas receive innervation from two or more different monoamine systems. For example, the neostriatum receives major innervation from the nigrostriatal (and to a less extent the mesolimbic) DA pathway, the ventral NA pathway and the more lateral 5-HT pathway. Evidence has been accumulating that this anatomical overlapping reflects functional interactions between all three transmitter systems. This will be discussed in more detail in the next section.

4. THE ROLE OF MONOAMINE SYSTEMS IN THE REGULATION OF EXPLORATORY, STEREOTYPED AND LOCOMOTOR BEHAVIOUR

A variety of methods have been used to attempt to study the roles of monoamine systems in regulating the three types of behaviours under consideration. Assessment of the results of such experiments is made difficult by the different techniques used in observing the behaviours. In addition a variety of animal species has been used. Even when these factors are taken into consideration it is still often difficult to account for the frequent differences between the observations of different workers.

The studies reviewed in this section can be broadly grouped into two types:

(i) observations of the effects of systemically administered drugs on normal animals, and

(ii) observations of the effects of stereotactic manipulations of discrete neuronal pathways and their terminal areas in the brain by lesioning and by

direct application of transmitters and of psychoactive drugs.

Except where otherwise stated the studies reviewed involve observations on rats and mice.

A. MONOAMINE NEURONAL INTERACTIONS

The effects of drugs in intact animals on monoamine systems can never be regarded as specific even if evidence is obtained that the drug has direct effects on only one system. This probably applies equally to the effects of "specific" lesions. It was mentioned at the end of the preceding section that the three monoamine systems are closely related anatomically, particularly in their projections. With the help of the newer techniques such as autoradiography and horseradish peroxidase injection more direct anatomical relationships have also been demonstrated. Serotonergic input into the locus coeruleus from raphe nuclei has been convincingly demonstrated (Bobillier et al. 1978; Descarries and Leger, 1978; Pickel et al. 1978; Sakai et al. 1978). Serotonergic projections to the substantia nigra and certain other DA cell body groups and to terminal areas for DA and NA projections (Bobillier et al. 1978) have also been observed.

Close relationships also exist between monoamine and other systems, especially cholinergic pathways (Jacobowitz and Palkovits, 1978) and pathways containing the neurotransmitter γ-aminobutyric acid (GABA) (Roberts, 1978).

There is an increasing body of evidence that these anatomical relationships represent functional interactions.

The best known example of this is the inter-action between cholinergic and dopaminergic systems which appear to act in antagonistic fashion in the neostriatum (Bartholini et al. 1973), and this forms a rationale for the use of anti-cholinergic drugs in the treatment of Parkinsonism (Barbeau, 1962; Calne, 1970), although it is now known that these drugs also inhibit neuronal uptake of DA (Coyle and Snyder, 1969) which may contribute to their beneficial action. Biochemical studies have shown that activation and inhibition of DA systems will produce opposite effects on striatal cholinergic function (Ladinsky et al. 1978). Interestingly, cholinergic function in the mesolimbic DA system is not altered in this way (Ladinsky et al. 1978) and this may explain the preferential effects on mesolimbic DA turnover by neuroleptic drugs with high antimuscarinic activity (see page 8).

Biochemical as well as behavioural evidence for a functional interaction between DA and 5-HT inputs into the striatum is well-documented. Lesions of the mesencephalic raphe nuclei which contain the cell bodies of serotonergic (5-HT) neurones reduce the stereotyped behaviour induced by dopamine agonists (Costall et al. 1975a). Dorsal but not median raphe nuclei lesions leads to a reduction in striatal homovanillic acid (HVA) levels, indicating a decreased turnover of DA (Samanin et al. 1978). L-tryptophan administration causes a rise in HVA levels while p-chlorophenylalanine, an inhibitor of tryptophan hydroxylase causes a reduction (Samanin et al. 1978). These latter findings have been interpreted as indicating

that 5-HT inputs facilitate DA inputs into the striatum. However, if the two systems were mutually antagonistic, reduction in activity in 5-HT systems might lead to a reduction in DA activity by inhibitory feedback control, as a compensatory mechanism. Direct antagonistic effects of 5-HT on the behavioural response to DA have been demonstrated following direct application of these drugs into the nucleus accumbens (Costall et al. 1976).

Serotonergic inputs from raphe nuclei appear to inhibit activity of noradrenergic cell bodies in the locus coeruleus (Pujol et al. 1978).

Antagonists of the α-adrenoceptor type inhibit activity of raphe 5-HT neurons, this effect being an indirect one, presumably by alterations in NA system activity (Gallager and Aghajanian, 1976).

There is also some evidence that NA neurons may influence activity in DA systems. Pharmacological manipulation of NA systems with α-noradrenergic adrenoceptor agonists and antagonists leads to changes in DA turnover (Anden and Grabowska, 1976). Unilateral lesions in the locus coeruleus lead to amphetamine and apomorphine-induced circling behaviour which is inhibited by DA, but not NA receptor blockade and appears to be mediated through the nigro-striatal system (Pycock et al.1976).

Connections between GABA and DA systems are well-documented. The output pathways from the neostriatum to the globus pallidus and substantia nigra, are GABAergic. (Hattori et al. 1973; Garcia-Munoz et al. 1977). There is still argument as to whether the striato-nigral pathway

plays a role in the feedback control of nigro-striatal dopaminergic activity (Garcia-Munoz et al. 1977).

A few biochemical and behavioural studies have been quoted above to illustrate interactions between different systems. The important fact to bear in mind is that no matter how specific the direct effects of a drug (or a lesion), these effects may lead to secondary changes in other systems because of these interactions. It may therefore be difficult to draw conclusions regarding any specific monoamine system from the observed effects. For instance, apomorphine, an alleged specific DA agonist (Ernst, 1967; Anden et al. 1967a), causes changes in 5-HT systems which appear to arise from the interaction between DA and 5-HT systems (Grabowska et al. 1975, 1976). While it is generally believed that the DA receptor activation is of primary importance, we cannot ignore the possibility that secondary effects on the serotonergic systems may contribute to, or even primarily mediate, the final response to the drug.

B. STUDIES OF THE EFFECTS OF SYSTEMICALLY ADMINISTERED DRUGS IN NORMAL ANIMALS

There are now available many drugs which are known to have marked actions on monoamine systems. The investigations of the effects of these drugs on the behavioural patterns monitored in the present study are extensive. It is therefore necessary to be somewhat selective in reviewing the large body of information available, emphasis being laid on those studies more directly related to the present one.

Amphetamines and Related Sympathomimetic Amines

Of these drugs amphetamine is most probably the one most widely studied. This drug has a number of actions on all three types of monoaminergic neurons. It releases DA (Besson et al. 1969; Voigtlander and Moore, 1973; Moore, 1977) NA (Carr and Moore, 1969; Carlsson, 1970; Moore, 1977) and to a less extent 5-HT (Azzarro and Rutledge, 1973; Moore, 1977) from neurones. Particularly at higher doses, amphetamine also inhibits neuronal monoamine uptake (Glowinski, 1970; Horn et al. 1974) and may also inhibit monoamine oxidase (Glowinski, 1970) although there is some doubt about the latter effect (Rutledge, 1970). A direct agonist action on monoamine receptors has also been claimed (Feltz and de Champlain, 1973).

In view of its lack of selective action on any type of monoamine neurone it is at first surprising that the drug is still so widely used experimentally. This is probably because its extremely potent effects on behaviour are very reproducible. Evidence regarding the roles of specific monoamine systems can be obtained by modifying the amphetamine actions with other, more specific drugs. Amphetamine is of added interest because of its psychotogenic effects (see page 8).

On its own, amphetamine at low doses stimulates locomotor behaviour in rats, mice and a variety of other animals (e.g. Del Rio and Fuentes, 1969; Fuxe and Ungerstedt, 1970; Kelly et al. 1975; Ljungberg and Ungerstedt, 1976). It also increases exploratory behaviour (Boissier and Simon, 1964; Bradley et al. 1968; Fuxe and

Ungerstedt, 1970; Ljungberg and Ungerstedt, 1976; Makanjuola et al. 1977b). As the dose is increased this locomotor and exploratory stimulation is replaced by stereotyped behaviour (Randrup et al. 1963; Del Rio and Fuentes, 1969; Fog, 1969; Fuxe and Ungerstedt, 1970; Randrup and Munkvad, 1974; Makanjuola et al. 1977b). In rats this stereotypy consists of sniffing and repetitive head and upper limb movements. As the stereotypy becomes more intense persistent biting, gnawing and licking also take place.

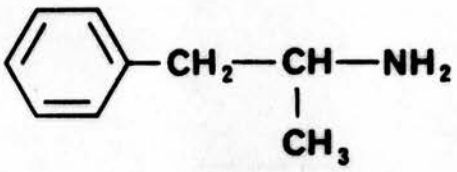
Some studies however, have indicated only a reduction in exploratory behaviour even with the lower doses of amphetamine (File, 1977) and there is some evidence that if the form of exploratory behaviour monitored is independent of locomotor behaviour then exploratory behaviour is actually reduced by amphetamine (Kumar, 1969; Robbins and Iversen, 1973).

Amphetamine derivatives, and related sympathomimetic drugs which have broadly similar actions on monoamine systems, produce similar behavioural effects. Certain derivatives, however, exercise differential effects on different monoamine systems and produce different behavioural responses. For example fenfluramine, (Fig. 4) is said to preferentially affect 5-HT systems, with less potent actions on catecholamine systems (Costa et al. 1971; Garrattini et al. 1975; Reuter, 1975; Kannengeisser et al. 1976). The drug may even block DA receptors (Garrattini et al. 1975). Most studies have failed to demonstrate locomotor stimulant effects or stereotypy with fenfluramine (Le Douarec and Neveu, 1970; Ziance et al. 1970; Costa et al. 1971;

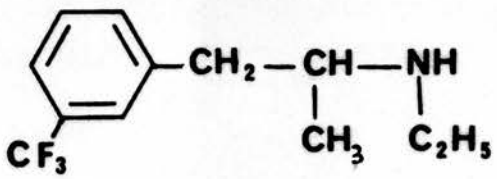
Lindquist and Gotestam, 1977) although there are reports of locomotor stimulation (Everritt and Hacket, 1972) and stereotypy (Taylor et al. 1973) at high dosage. Such observations demonstrate that examination of the behavioural effects of drugs with more specific effects on one system might indeed be rewarding. In this respect, it has been demonstrated that the different potencies of D- and L-amphetamine on locomotor stimulation and induction of stereotyped behaviour correlate with the relative potencies of these isomers to stimulate DA and NA systems, the D-isomer being more potent in effects on NA systems and in inducing locomotor stimulation (Taylor and Snyder, 1971; Scheel-Kruger, 1971). It was concluded by these workers that stimulation of DA systems was the important element in the production of stereotyped behaviour whereas NA systems were concerned with the effects on locomotor behaviour.

Drugs with agonist actions on monoamine receptors

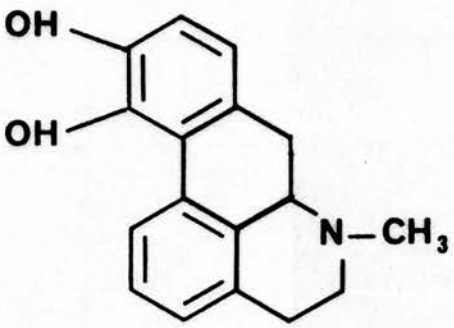
Studies with drugs that have more selective effects in stimulating individual monoamine systems all yield evidence strongly implicating dopaminergic systems in the mediation of all three behaviours. Apomorphine and its derivatives (Fig. 4), and other DA receptor agonist drugs such as bromocryptine, stimulate both locomotor behaviour (usually at lower doses) and stereotypy (Ernst, 1967; Fog, 1969; Ungerstedt, 1974; Ljungberg and Ungerstedt, 1976; Johnson et al. 1976; Dolphin et al. 1977). In our previous study (Makanjuola, 1976; Makanjuola et al. 1977b) it was found that at low doses apomorphine induced a form of exploratory behaviour involving olfactory and gustatory



Amphetamine



Fenfluramine



Apomorphine

FIG. 4

sensation whereas larger doses converted this behaviour into a stereotyped form. There is considerable evidence that apomorphine and bromocryptine interact with post-synaptic DA receptors (Ernst, 1967; Andén et al. 1967a; Johnson et al. 1976; Seeman et al. 1978). Changes in 5-HT and NA systems are probably induced indirectly through interactions between DA systems and NA and 5-HT systems (Grabowska et al. 1975, 1976; Snider et al. 1975; Maj, 1977).

There are no entirely satisfactory specific 5-HT receptor stimulants. Lysergic acid diethylamide (LSD) is claimed to act centrally as a 5-HT receptor agonist, its predominant action being a direct inhibition of 5-HT neurones (Aghajanian & Haigler, 1974 ; Aghajanian et al. 1975). There is evidence that LSD can also activate DA receptors (Kelly and Iversen, 1975). Contradictory findings on exploratory and locomotor behaviour are reported for LSD (Davis and Redfern, 1973; Hughes, 1973; Kelly and Iversen 1975) and behavioural effects similar to those of 5-methoxy-N,N,-dimethyltryptamine have also been claimed (Fog, 1969; Jacobs, 1976). 5-Methoxy,-N,N,-dimethyltryptamine (5-MEODMT), which appears to act as an agonist on 5-HT receptors (Green and Grahame-Smith 1976) produces a bizarre hyperactivity syndrome identical to that seen after administration of amino acid precursors of 5-HT in the presence of monoamine oxidase inhibition (see page 30). Quipazine, another 5-HT receptor agonist, produces in rats an atypical form of stereotypy, similar to the behavioural response to 5-MEODMT, which is reduced or abolished by 5-HT receptor antagonists but not DA receptor

antagonists and is abolished by lesions of the mesencephalic raphe nuclei (Costall and Naylor 1975b). Pre-synaptic actions may therefore contribute to its effects.

Stimulation of central noradrenergic receptors leads to less clear-cut results. Clonidine is an α-adrenoceptor agonist (Anden et al. 1970b), and it also diminishes neuronal NA release, probably by activation of α-adrenoceptors on the noradrenergic neuronal membranes (Starke and Matel, 1973; Andén et al. 1976). Clonidine also stimulates 5-HT systems (Maj et al. 1975). Given systemically the drug causes motor sedation (Pycock et al. 1977; Zebrowska-Lupina et al. 1977) although locomotor stimulation has also been observed in satiated rats (Bednarczyk and Vetulani, 1977). Following destruction of central catecholamine neurones by intraventricular 6-hydroxydopamine, Zebrowska-Lupina et al. (1977) found that clonidine induced locomotor stimulation in reserpine-pretreated rats. This locomotor stimulation was inhibited by central α-adrenoceptor blockade but not by neuroleptic drugs. These authors claimed that the locomotor stimulation was induced because the inhibitory effect on NA release as a result of its activation of pre-synaptic adrenoceptors was no longer possible and thus the locomotor stimulant actions resulting from interaction with postsynaptic α-adrenoceptors was unmasked. This suggestion would assume that there is a relatively high basal level of noradrenergic activity. Further evidence in support of this hypothesis might be provided by examination of the effects of selective pre- and post-synaptic α-adrenoceptor antagonists on the

behavioural actions of clonidine.

In nialamide-pretreated rats given L-DOPA into the lateral cerebral ventricles clonidine inhibited the phase of locomotor stimulation associated predominantly with biochemical effects on NA systems (Bednarczyk and Vetulani, 1977) presumably because of its pre-synaptic actions. Clonidine induced exploratory behaviour in reserpinized rats that were also given apomorphine (Fuxe and Ungerstedt, 1970), and enhanced apomorphine-induced locomotor activity in reserpinized mice (Andén and Strombom, 1974; Pycock et al. 1977).

Monoamine Precursor Administration

Increased activity in individual monoamine systems can be achieved by treatment with appropriate amino-acid precursors which are converted intraneuronally into the monoamine transmitters. This increase in transmitter concentrations is greatly enhanced by pretreatment with a monoamine oxidase inhibitor. This has been demonstrated for L-tryptophan and L-5-hydroxytryptophan (5-OHTP) which lead to increased 5-HT formation (Moir and Eccleston 1968; Grahame-Smith, 1971a,b), as well as L-DOPA (L-dihydroxy-phenylalanine) which increases formation of DA and, to a lesser extent, NA (Butcher and Engel, 1969; Stromberg and Svensson, 1970; Dolphin et al. 1975; Green and Kelly 1976).

L-Tryptophan administration produces selective increases in 5-HT synthesis in 5-HT neurones leaving the synthesis of catecholamines unaffected (Moir and Eccleston, 1968; Grahame-Smith 1971a) because of the restricted

localization of tryptophan hydroxylase to serotonergic neurones. In contrast, the decarboxylase enzyme catalysing the conversion of L-DOPA and 5-OHTP to the corresponding amine is present in both serotonergic and catecholaminergic neurones and shows no selectivity between the precursor amino-acids (Garrattini and Valzelli, 1965; Musacchio, 1975). Amine formation from these precursor amino-acids can therefore take place in both types of neurone. Administration of L-DOPA thus leads to the appearance of dopamine in serotonergic neurones with an accompanying fall in the concentration of the normal transmitter, 5-HT. The contrary situation occurs after administration of 5-OHTP (Butcher et al. 1972). As Moir and Eccleston (1968) have shown for dog's brain, the administration of 5-OHTP and of L-tryptophan lead to elevated 5-HT concentrations, but the pattern conformed to the normal distribution of 5-HT only with the latter.

Given without monoamine oxidase inhibition, L-tryptophan or L-5-hydroxytryptophan cause only motor sedation in mice and rats (Brown, 1960; Modigh, 1972, 1973; Jacobs et al. 1974). After pretreatment with a monoamine oxidase inhibitor, administration of L-tryptophan or L-5-hydroxytryptophan leads to a characteristically exceedingly bizarre behavioural syndrome consisting of hyperactivity, abnormal limb movements, tremor, rigidity, hyperactivity, stereotyped head movements including lateral movements as well as nodding, and tail rigidity and abduction (Grahame-Smith, 1971a,b; Jacobs et al. 1974; Jacobs, 1976; Green and Grahame-Smith, 1976). It must

be stressed that this behavioural syndrome cannot be related to quantitative changes in locomotion or exploration and any stereotypy is quite different in character from that seen with drugs such as amphetamine. Indeed, behaviour seems to be essentially disorganized. The syndrome is also elicited by the serotonergic receptor agonist 5-methoxy-N,N-dimethyltryptamine (Grahame-Smith, 1971b).

The syndrome produced by 5-HT agonists or by the combination of monoamine oxidase inhibition and amino-acid precursors of 5-HT is inhibited by neuroleptic drugs (but not by pimozide) (Grahame-Smith, 1971b; Jacobs, 1974a)and by serotonergic receptor blockade (Jacobs, 1974b) but not noradrenergic receptor blockade (Jacobs et al. 1974). The syndrome produced with 5-hydroxytryptophan or 5-methoxy-N,N-dimethyltryptamine is not blocked by pretreatment with p-chlorophenylalanine whereas that produced with L-tryptophan is (Jacobs, 1974; Grahame-Smith 1971b).

L-DOPA (L-dihydroxyphenylalanine) usually induces locomotor stimulation (Smith, 1963; Bartholini et al. 1969; Stromberg and Svensson, 1970; Kulkarni and Dandiya, 1974; Dolphin et al. 1976; Johnson et al. 1976; Ljungberg and Ungerstedt, 1976). Most studies using L-DOPA also employ peripheral decarboxylase inhibitors which potentiate the increase in central catecholamine synthesis as well as the motor effects (Bartholini et al. 1969; Bartholini and Pletscher, 1969; Butcher and Engel, 1969; Johnson et al. 1976; Molander and Randrup, 1974). The behavioural and

biochemical responses to L-DOPA are also potentiated by pretreatment with a monoamine oxidase inhibitor (Svensson and Waldeck, 1970). A mild form of stereotyped behaviour has been reported after L-DOPA administration at high dosage (Scheel-Kruger and Randrup, 1967; Ernst, 1972; Molander and Randrup, 1974; Johnson et al. 1976; Ljungberg and Ungerstedt, 1976).

Antagonists at monoaminergic receptors

Agents which block monoamine receptors also produce quite marked effects on behaviour. The neuroleptic drugs all have potent antagonistic activity on DA receptors which is now thought to be responsible for the induced responses (Andén et al. 1970a; Carlsson, 1974, 1978; Seeman et al. 1976). They also have varying, usually minor, degrees of blocking action on NA receptors (Andén et al. 1970a) and possibly on 5-HT receptors (Leysen et al. 1976). Neuroleptic drugs inhibit locomotion and exploration (Ryall, 1958; Janssen et al. 1960; Boissier and Simon, 1964; Kumar, 1971b; Nakama et al. 1972; File, 1973). Reserpine, which depletes all three types of monoamine neurones of their transmitter (see page 4), also inhibits locomotor behaviour and exploration (Ryall 1958; Boissier and Simon, 1964; Fuxe and Ungerstedt, 1970). The inhibition of exploration by these drugs may be secondary to the locomotor impairment (Battig, 1969; Shillito, 1970).

Neuroleptic drugs also block the effects of amphetamine and related sympathomimetic agents and of L-DOPA and DA receptor agonists such as apomorphine and bromocryptine

in stimulating exploration, locomotor behaviour and stereotypy (Randrup et al. 1963; Del Rio and Fuentes, 1969; Costall and Naylor, 1974b,c; Ljungberg and Ungerstedt, 1976). In a previous study (Makanjuola,1976; Makanjuola et al. 1977b) it was found that high doses of haloperidol prevented both amphetamine-induced exploratory and stereotyped behaviour, while a very small dose blocked only the stereotypy, leaving some exploratory behaviour to continue.

It has been demonstrated that drugs such as clozapine and thioridazine, which show differential effects by blocking activity in the mesolimbic DA system more than of the nigrostriatal system (see page 8) are more effective in inhibiting drug-induced locomotor activity than stereotyped behaviour whereas on the other hand other DA antagonists such as haloperidol, pimozide and chlorpromazine which show no such differential actions are equally effective on both forms of behaviour (Costall and Naylor, 1975d; Delini-Stula, 1976; Ungerstedt et al. 1977). Such differences between the neuroleptic drugs are further exemplified by the responses following cessation of chronic treatment. After withdrawal of thioridazine and clozapine, but not of haloperidol, there is an increase in spontaneous and apomorphine-induced locomotor activity; stereotyped behaviour induced by apomorphine is potentiated after withdrawal from all three drugs (Smith and Davis, 1976).

The effects of reserpine on drug-induced behavioural changes are rather complex. This drug has been widely observed to have no effect on amphetamine-induced

stereotyped behaviour (Randrup et al. 1963; Fuxe and Ungerstedt, 1970; Scheel-Kruger, 1971), although in one study a reduction in amphetamine-induced stereotypy by reserpine was observed (Herman, 1967). It was claimed that this is because amphetamine exerts its transmitter-releasing effects on a pool of newly-synthesized dopamine (Scheel-Kruger, 1971; Moore, 1977). Tyrosine hydroxylase inhibition by α-methyl-p-tyrosine which should profoundly affect such a pool, does inhibit amphetamine-induced stereotyped behaviour (Scheel-Kruger, 1971). Certain other sympathomimetic drugs e.g. methylphenidate, were thought to exert their actions through a more long-term catecholamine pool since their stereotypy-inducing actions were blocked by reserpine but not α-methyl-p-tyrosine (Scheel-Kruger, 1971). The stimulant actions of amphetamine administration on locomotion and exploration are inhibited by reserpine pretreatment in rats (Fuxe and Ungerstedt, 1970; Scheel-Kruger, 1971) but not in mice (Thornburg and Moore, 1973). The former finding was explained on the basis that noradrenergic systems played a major role in regulating these two behaviours and that the NA pool on which amphetamine acted was sensitive to the depleting effects of reserpine (Fuxe and Ungerstedt, 1970; Scheel-Kruger, 1971). Acute reserpine pretreatment may potentiate apomorphine-induced stereotypy in rats (Rotrosen et al. 1972; Costall and Naylor, 1973; Wallach, 1974; Mogilnicka and Braestrup, 1976) possibly because of the development of DA receptor supersensitivity or alternatively because of the removal of opposing influences from other monoamine systems.

α -Adrenoceptor blocking agents may cause a decrease in spontaneous locomotor activity (Ljungberg and Ungerstedt, 1976) and also a reduction in the exploratory and locomotor stimulation induced by amphetamine (Fuxe and Ungerstedt, 1970; Rolinski and Scheel-Kruger, 1973; Ljungberg and Ungerstedt, 1976) and by L-DOPA (Andén et al. 1977). α -Adrenoceptor blockade either does not affect drug-induced stereotyped behaviour (Randrup et al. 1963; Herman, 1967; Del Rio and Fuentes, 1969) or may even potentiate it (Ljungberg and Ungerstedt, 1976; Mogilnicka and Braestrup, 1976). This potentiation may be caused by the reduction of the locomotor stimulant effects of the drugs. It must be emphasized that α -adrenoceptor blockade produces marked peripheral changes including circulatory collapse which are bound to affect behaviour. In addition their effects may be relatively non-specific. Phenoxybenzamine and other haloalkylamines for example, in addition to blocking α -adrenoceptors (Andén et al. 1967b; Doxey et al. 1972) also block 5-HT, histamine and acetylcholine receptors (Nickerson and Collier, 1975). α -Adrenoceptor antagonists also differ in the relative selectivity of their actions on pre- and post-synaptic receptors (Doxey et al. 1972; Starke et al. 1975). Agents which block β -adrenoceptors have no effect on stereotyped behaviour (Randrup et al. 1963) or reduce it (Herman,1967).

Little information is available regarding the effects of 5-HT receptor blockade, e.g. with methysergide or cyproheptadine, on spontaneous or drug-induced locomotor and exploratory behaviour. Inhibition of spontaneous but

not amphetamine-induced locomotor behaviour in mice has been observed (Van Riezen, 1972). Most studies have failed to demonstrate an effect on apomorphine-induced or amphetamine-induced stereotyped behaviour (Randrup et al. 1963; Randrup and Munkvad, 1964; Rotrosen et al. 1972; Baldesarini et al. 1975; Rolinski, 1977), although potentiation has been reported (Weiner et al. 1973).

Monoamine transmitter synthesis inhibition

Drugs which inhibit monoamine transmitter synthesis may have marked behavioural effects. α-Methyl-p-tyrosine, a tyrosine hydroxylase inhibitor, causes marked behavioural sedation and prevents the stimulation of all three behaviours by amphetamine (Ernst, 1967; Arnfred and Randrup, 1969; Scheel-Kruger, 1971; Randrup and Scheel-Kruger, 1973; Thornburg and Moore, 1973), while there is no effect on apomorphine-induced stereotypy (Rotrosen et al. 1972); this is evidence for the indirect nature of the actions of amphetamine in contrast to the direct receptor activating effects of apomorphine.

Dopamine-β-hydroxylase inhibitors, which preferentially inhibit NA synthesis, have been found to reduce spontaneous locomotor and exploratory activity (Mayer and Eybl, 1973; Vetulani et al. 1973) or to have no effect (Ljungberg and Ungerstedt, 1976). They reduce but do not abolish locomotor and exploratory behaviour induced by amphetamine (Mayer and Eybl, 1973; Khalsa and Davis, 1975; Ljungberg and Ungerstedt, 1976) although one study could not demonstrate any effect (Thornburg and Moore,1973). L-DOPA-induced locomotor stimulation is also decreased but

not abolished (Svensson and Waldeck, 1970; Stromberg and Svensson, 1971; Molander and Randrup, 1974; Dolphin et al. 1976; Andén et al. 1977), but again some workers have failed to observe any effect (Scheel-Kruger and Randrup, 1967).

As with α-adrenoceptor blockade, dopamine - β - hydroxylase inhibition has been reported to have no action on drug-induced stereotyped behaviour or to potentiate it (Randrup and Scheel-Kruger, 1966; Mayer and Eybl, 1973; Ljungberg and Ungerstedt, 1976; Mogilnicka and Braestrup, 1976).

Depletion of 5-HT neurones of their transmitter by parachlorophenylalanine or p-chloroamphetamine usually leads to increases in spontaneous exploratory and locomotor activity (Chrusciel and Herman, 1969; Fibiger and Campbell, 1971; Jacobs et al. 1975a; Segal, 1976; Marsden and Curzon, 1977) although in a few studies no effect (Breese et al. 1974) or an inhibition has been observed (Vorhees et al. 1975). These drugs also potentiate the locomotor stimulant actions of amphetamine (Mabry and Campbell, 1973; Breese et al. 1974; Segal, 1976) but usually have little effect on amphetamine - or apomorphine-induced stereotypy (Rotrosen et al. 1972; Breese et al. 1974; Baldesarini et al. 1975; Segal, 1976). In one study a potentiation of amphetamine-induced stereotypy by p-chlorophenylalanine was obtained but this was not modified by 5-hydroxytryptophan administration (Baldesarini and Griffith, 1976).

Antidepressant drugs

Antidepressant drugs are known to exert profound

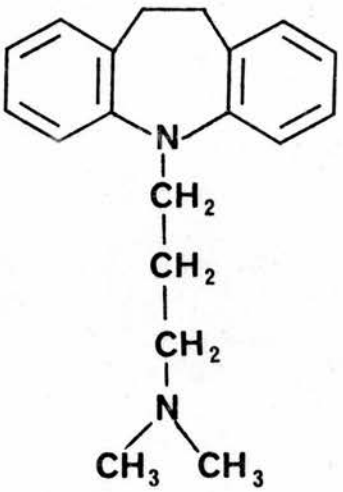
effects on monoamine systems. Monoamine oxidase inhibitors are extensively used as pharmacological tools in the study of behaviour and in biochemical pharmacology. Certain problems limit their use in examining the roles of specific monoamine systems. They have significant effects on the rate of metabolism of psychoactive drugs and other substances (Boakes, 1974; Ho, 1972). We are also a long way from finding a usable drug with effects on only one system. Although this seemed a possibility with the alleged demonstration of multiple forms of monoamine oxidase with some selectivity for different substrates (Neff and Yang 1974; Youdim, 1974), it has been suggested that the results may be artefactual (Jain, 1977).

On first consideration monoamine neuronal uptake inhibitors would appear to provide useful tools in the study of monoamine systems. The antidepressant drugs of this group known collectively as the tricyclics exert effects on both NA and 5-HT uptake mechanisms in their respective neurones, although some are slightly more effective on the one than the other. For example, desmethylimipramine and nortriptyline (Fig. 5) are more effective inhibitors of NA uptake while imipramine and amitriptyline are more effective on 5-HT uptake (Iversen, 1975; Schacht et al. 1977). These drugs are relatively ineffective in inhibiting DA uptake (Horn et al. 1971; Iversen, 1975). Recently compounds with much more selective actions have been introduced. Chlorimipramine and zimelidine (Fig. 5) are much more potent inhibitors of 5-HT uptake than of NA uptake (Ross and Renyi, 1977;

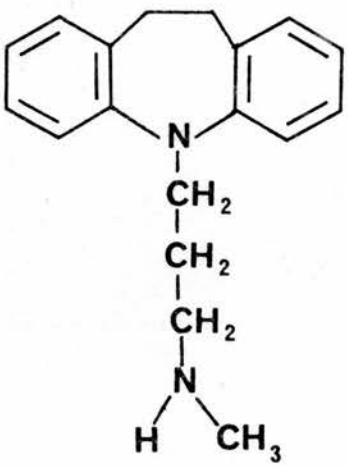
Waldmeier et al. 1976). The recently introduced drug nomifenzine is a potent inhibitor of DA as well as NA uptake and has minimal effects on 5-HT uptake (Hunt et al. 1974; Schacht et al. 1977).

In general, monoamine uptake inhibitors with actions on NA and 5-HT systems have little effect on behaviour. Most cause sedation and varying, usually slight, reduction of motor activity (Sulser et al. 1962; Klerman and Cole, 1965; Kulkarni and Dandiya, 1974; Spencer, 1977). Nomifensine, which inhibits DA as well as NA uptake has very potent locomotor stimulant properties, and at high dosage will induce stereotyped behaviour (Braestrup and Scheel-Kruger, 1976; Costall and Naylor, 1977; Hoffman, 1977). It would appear that it is the effects on DA systems that are important for these actions since they do not occur with compounds which inhibit NA or 5-HT uptake only.

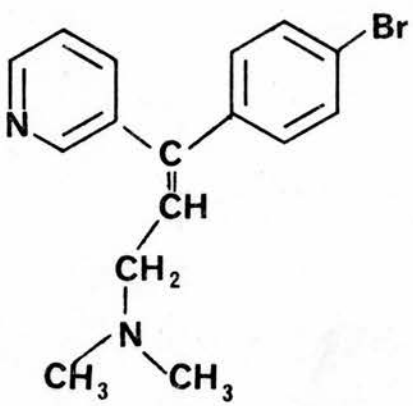
Uptake inhibitors might also provide specific tools for modifying the effects of other drugs. The interaction of amphetamine with tricyclic drugs has been much studied in this respect and the ability of uptake inhibitors to potentiate the locomotor stimulant and stereotypy-inducing effects of amphetamine now appears to be part of the general test battery employed during pharmacological evaluation of uptake inhibitors. These drugs potentiate a variety of behavioural effects of amphetamine (Carlton, 1961; Sulser et al. 1966; Stein and Sifter, 1961; Spencer, 1977). The monoamine uptake inhibitors do not appear to have been compared systematically to attempt to correlate these



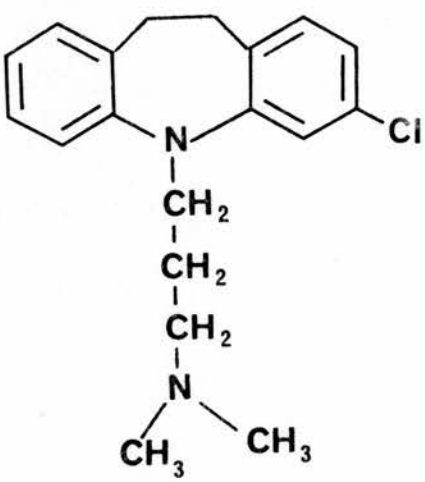
Imipramine



Desmethylimipramine



Zimelidine



Chlorimipramine

FIG. 5: Some neuronal monoamine uptake inhibitors.

changes in terms of activity on uptake of specific monoamines. It was originally believed that this potentiation of amphetamine effects was caused by prevention of the reuptake of monoamines released by amphetamine, in which case the effects might indeed provide a useful method of studying specific monoamine systems. However, it has been shown that tricyclic uptake inhibitors also prevent metabolism and inactivation of amphetamine in the liver, mainly by preventing ρ-hydroxylation for which process the tricyclic drugs compete (Sulser et al. 1966; Lewander, 1968; Valzelli et al. 1968; Garrattini et al. 1976). The marked potentiation of amphetamine effects seems to be a property common to all neuronal uptake inhibitors, including several that are structurally unrelated to tricyclic compounds and which could not be in competition for the p-hydroxylation process. Moreover, the behavioural effects of amphetamine are mediated predominantly by dopamine systems and most of the uptake inhibitors are relatively ineffective on DA uptake.

Much more information might be gained by testing the effects of the newer drugs as well as the conventional "tricyclic" drugs on amphetamine metabolism, to see whether the potencies of a variety of these drugs on amphetamine metabolism correlate with their potencies in potentiating the behavioural effects of amphetamine.

C. STEREOTACTIC MANIPULATION OF MONOAMINE PATHWAYS

Much attention has focussed recently on the relative importance of the nigrostriatal and mesolimbic DA systems in the mediation of locomotor and stereotyped behaviour.

Less attention has been paid to the roles of NA and 5-HT systems. In the context of manipulation of individual pathways, exploratory behaviour has been largely ignored. The individual pathways can be manipulated either by lesioning them at different points between origin and termination or by injecting transmitters or psychoactive drugs into terminal areas. In general, lesioning of cell body groups or terminal areas provides more specific information than lesions in the intermediate pathways because of the close interrelationships of different systems and of individual subsystems as they ascend, for example, in the medial forebrain bundle. In this respect the use of specific neurotoxins such as 6-hydroxydopamine or the toxic dihydroxytryptamines allows selective lesioning of one particular type of monoamine neurone, but even then no distinction will be possible between individual sub-systems subserved by the same transmitter. It is however possible in some cases to lesion selectively individual pathways near their origins or termination.

Dopaminergic Systems

During the last decade, two bodies of opinion have emerged as to the behavioural roles of the nigro-striatal and the mesolimbic DA systems. Many workers believed that the mesolimbic system was involved in the mediation of drug-induced locomotor stimulation whereas the nigro-striatal system was involved in stereotypy (e.g. Kelly et al. 1975). Costall and his colleagues (e.g. Costall and Naylor, 1974a) held the opposite view. Gradually the two schools of thought have converged, mainly as a result of

some accommodation on the part of Naylor and his colleagues.

When reviewing the effects of DA pathway lesions on behaviour it is necessary to make a distinction between lesions induced with 6-hydroxydopamine (6-OHDA) and those by electrolytic or other physical means. 6-Hydroxydopamine is a specific toxin to catecholamine neurones (Ungerstedt, 1971e; Javoy et al. 1975) and its injection will produce degeneration in DA and NA neurones only. Destruction of noradrenergic fibres by 6-OHDA can be prevented by blocking its uptake into noradrenergic neurones with desmethylimipramine or protriptyline (Iversen and Kelly, 1975; Roberts et al. 1975). Destruction of the dopaminergic neurones is followed by the development of supersensitivity of post-synaptic DA receptors. (Ungerstedt, 1971c; Ungerstedt and Marshall, 1975). Following a 6-OHDA lesion, therefore, there should be a potentiation of the effects of drugs such as apomorphine which act post-synaptically on DA receptors and an inhibition of the effects of drugs such as amphetamine which act presynaptically. This has been conclusively demonstrated (e.g. Ungerstedt, 1971c;d; Kelly et al.1975). Any 6-OHDA lesion which does not induce these opposite effects with apomorphine and amphetamine must be suspect.

Electrolytic lesions will destroy all fibres and cell bodies in the area, including afferent and efferent fibres and fibres of passage. Very different effects might therefore follow from those seen with 6-OHDA, and apomorphine and amphetamine should produce the same behavioural responses following electrolytic lesions.

While it is now generally believed that drug-induced stereotyped behaviour is mediated by the nigro-striatal pathway, most studies have failed to demonstrate any effect on apomorphine - or amphetamine-induced stereotypy following electrolytic lesions of the substantia nigra (Iversen, 1971; Simpson and Iversen, 1971) or of the caudate-putamen (McKenzie, 1972; Divac, 1972; Costall and Naylor, 1973a, 1974a). One study demonstrated abolition of apomorphine-induced but not amphetamine-induced stereotyped behaviour following lesions in the substantia nigra (Costall et al. 1972). Apomorphine- and amphetamine-induced stereotypy is drastically reduced or abolished following electrolytic lesions of the globus pallidus (Naylor and Olley, 1972; Costall and Naylor, 1973a,1974a; Costall et al. 1975a). It should be remembered that the globus pallidus receives projections from the nucleus accumbens (Conrad and Pfaff, 1976) as well as from the neostriatum (Szabo, 1970; Garcia-Munoz et al. 1977). A few studies have demonstrated a reduction in amphetamine-induced stereotyped behaviour following electrolytic lesions of the caudate-putamen (Naylor and Olley, 1972; Neill et al. 1974).

A 6-hydroxydopamine lesion of the substantia nigra usually blocks amphetamine-induced stereotypy and enhances apomorphine-induced stereotypy (Ungerstedt, 1971d; Creese and Iversen, 1972, 1975; Fibiger et al. 1973; Price and Fibiger, 1974; Brook and Iversen, 1975). It should be remembered that 6-OHDA lesions of the substantia nigra may also affect dopaminergic fibres of the ascending

mesolimbic system which pass nearby. Electrolytic lesions may, additionally, damage the striato-nigral pathway (see Garcia-Munoz et al. 1977). 6-Hydroxydopamine lesioning of the caudate-putamen enhances apomorphine-induced stereotypy while preventing amphetamine-induced stereotypy (Asher and Aghajanian, 1974; Creese and Iversen, 1974; Kelly et al. 1975).

Most studies have shown that 6-OHDA or electrolytic lesions of the caudate-putamen and substantia nigra do not affect apomorphine-induced or amphetamine-induced locomotor stimulation, (Naylor and Olley, 1972; Creese and Iversen, 1972; Costall and Naylor, 1973e; Neill et al. 1974; Brook and Iversen, 1975; Kelly et al. 1975), although a reduction in amphetamine-induced locomotor stimulation following 6-OHDA or electrolytic lesions of the substantia nigra has been observed (Iversen, 1971; Simpson and Iversen, 1971; Creese and Iversen, 1975; Roberts et al. 1975). The problems of lack of selectivity with substantia nigra lesions have already been pointed out.

There are also differing claims regarding the effects of lesions of mesolimbic pathways. Iversen and her colleagues (Creese and Iversen, 1974; Kelly et al. 1975; Kelly and Iversen, 1976) found that 6-hydroxydopamine lesions of the accumbens nuclei, which also affected the olfactory tubercles, prevented the locomotor stimulant actions of amphetamine while potentiating the locomotor stimulant effects of apomorphine. However Naylor and his colleagues using electrolytic lesions of various terminal areas of the mesolimbic DA system obtained quite

different results (Costall and Naylor, 1973a,1974a,1974b; Costall et al. 1975a). These workers found that lesions in these areas produced effects predominantly on stereotyped behaviour induced by amphetamine and apomorphine. Lesions of the accumbens nuclei and olfactory tubercles abolished the 'low intensity' components of sniffing and head movements. Lesions of the central nucleus of the amygdala abolished the 'high intensity' components of gnawing, biting and licking. One independent study confirmed that apomorphine-induced stereotypy was abolished by olfactory tubercle lesions (McKenzie, 1972).

Clearly, further experiments are needed to resolve these conflicting findings. In particular it may be rewarding to examine more carefully the effects of discrete lesions of different DA terminal areas in the mesolimbic system and of different parts of the caudate-putamen. It would be interesting to see the results of 6-OHDA and electrolytic lesions from the same laboratory and also to take further the contention of Naylor and his colleagues that different forms of stereotypy may be subserved from different anatomical loci.

Lesioning of the 'A10' DA nucleus has been found to cause sustained hyperactivity with diminished attention to the environment (Galey et al. 1977; Stinus et al. 1977). It is difficult to fit this in with the above findings regarding the destruction of terminal areas. The syndrome appears to be related to DA neuronal depletion in the frontal cortex (Tassin et al. 1978).

In summary, observations following 6-OHDA lesions indicate that amphetamine- and apomorphine-induced locomotor stimulation are mediated through the accumbens nuclei whereas stereotypy is mediated through the caudate-putamen. Observations following electrolytic lesions do not provide such clear-cut results but seem to suggest amphetamine- and apomorphine-induced stereotypy to be mediated through terminal areas in the mesolimbic dopaminergic system.

Further important evidence regarding the functional roles of the mesolimbic and nigrostriatal pathways has come from studies of the effects of application of monoamine transmitters and drugs to DA terminal areas in rats. Pijnenburg and van Rossum (1973) were the first to demonstrate that injection of dopamine into the nucleus accumbens causes locomotor hyperactivity in rats pretreated with a monoamine oxidase inhibitor; this was subsequently confirmed (Costall and Naylor, 1975c; Costall et al. 1975b; Jackson et al. 1975). The locomotor stimulation was noticed to be accompanied by continuous sniffing. Even without monoamine oxidase inhibition the locomotor response still occurred although it was less intense (Jackson et al. 1975; Pijnenburg et al. 1976). The response was blocked by neuroleptic drugs but not by NA receptor blocking agents (Jackson et al. 1975; Costall and Naylor, 1976; Pijnenburg et al. 1976). Injection of NA into the nucleus accumbens induced a slight locomotor stimulation only in nialamide-pretreated rats which was blocked by systemically administered haloperidol; α-noradrenergic blockade had

inconsistent effects (Pijnenburg and van Rossum, 1973; Jackson et al. 1975; Pijnenburg et al. 1976). 5-HT injection has been reported to produce either no behavioural change (Jackson et al. 1975) or a reduction in locomotor activity (Costall et al. 1976; Pijnenburg et al. 1976).

Bilateral application of an inhibitor of gamma-amino-butyric acid transaminase, ethanolamine-O-sulphate, to the globus pallidus or electrolytic lesions of the globus pallidus blocked the effect of DA applied to the nucleus accumbens (Pycock and Horton, 1976).

DA injection into the caudate-putamen has been shown to induce stereotyped behaviour, especially the high-intensity components of licking, biting and gnawing (Fog and Pakkenburg, 1971; Pijnenburg and Van Rossum, 1973; Costall et al. 1974a; Costall and Naylor, 1975a; Jackson et al. 1975). NA and 5-HT injection into the striatum did not result in behavioural changes (Costall et al. 1974; Jackson et al. 1975).

Application of apomorphine and its derivatives, or of amphetamine or L-DOPA into the neostriatum or nucleus accumbens has been reported to produce effects very similar to those of DA (Ernst and Smelik, 1966; Costall et al.1974; Costall et al. 1975a, 1975b; Jackson et al. 1975), although Pijnenburg et al. (1976) have found apomorphine injected into the nucleus accumbens to produce both stimulation and depression of locomotor activity; these different responses which occurred even in the same animals and were not dose related were inexplicable.

Injections of DA into the olfactory tubercles

produces similar effects to those of injections into the accumbens nuclei (Pijnenburg et al. 1975a). DA and apomorphine application to the central nucleus of the amygdala did not affect behaviour (Costall and Naylor, 1975a; Costall et al. 1975a, 1975b).

Neuroleptic agents injected directly into the nucleus accumbens has been reported to block the locomotor stimulant but not the stereotypy-inducing effects of amphetamine (Jackson et al. 1975; Pijnenburg et al. 1975b) while haloperidol injection into the neostriatum was found to block the stereotyped response to amphetamine (Fog & Pakkenburg, 1971; Costall et al. 1975a).

These observations regarding the effects of direct drug application to DA-rich areas lend further support to the idea that the nucleus accumbens and olfactory tubercle are concerned with the mediation of locomotor activity and "stereotyped sniffing" while the neostriatum is involved in the 'high intensity' components of stereotyped behaviour: gnawing, biting and licking. The consistent failure of Naylor and his colleagues to detect any behavioural changes following DA or apomorphine application to the central nucleus of the amygdala casts doubt on the relevance of their findings regarding the effects of lesions of that nucleus (page 45). The behavioural changes following lesions of this nucleus could be the indirect consequence of damage to fibres of passage or damage to neighbouring structures.

Noradrenergic (NA) Systems

Manipulations of NA systems have much less dramatic effects on behaviour than do manipulation of dopaminergic systems. Bilateral lesions of the locus coeruleus produced no effect on spontaneous activity or on the locomotor response to apomorphine or amphetamine (Pycock, 1977; Anlezark et al. 1973) and the same applies to the effects of selective lesioning of the ascending NA pathways (Roberts et al.1975; Creese and Iversen, 1975; Pycock, 1977). One study, however, did indicate a potentiation of amphetamine- but not apomorphine-induced stereotyped behaviour following lesions of ascending NA pathways (Braestrup, 1977) while another indicated a potentiation of apomorphine and amphetamine-induced stereotypy following locus coeruleus lesions (Kostowski et al. 1977).

The effects of NA injection into the nucleus accumbens and caudate-putamen have already been described (pages 46,47). These effects of manipulations of monoamine systems may be mediated through DA systems. Such an interaction has been amply demonstrated by the effects of unilateral locus coeruleus lesions. Such unilateral lesions of the locus coeruleus lead to contraversive circling behaviour under the influence of apomorphine or amphetamine; this turning appears to be related to indirect effects on the nigro-striatal DA system since it was unaffected by systemically administered α or β adrenoceptor blocking agents but abolished by DA receptor antagonists and reversed by ipsilateral substantia nigra lesions or injection of phenoxybenzamine into the ipsilateral substantia nigra (Pycock et al. 1975; Donaldson et al. 1976).

Serotonergic (5-HT) Systems

Manipulations of certain 5-HT pathways have been reported to produce clear-cut behavioural effects. Most

early work involved examination of the effects of combined lesions of the dorsal and median raphe nuclei (B7 and B8 cell groups). These lesions led to an increase in spontaneous locomotor and exploratory activity (Kostowski et al. 1968; Lorens et al. 1971, 1976; Srebro and Lorens, 1975) and an increase in the locomotor response to apomorphine and amphetamine (Neill et al. 1972; Grabowska, 1974; Geyer et al. 1976). More selective lesioning experiments showed that it was the median and not the dorsal nucleus lesion that was responsible for the increase in spontaneous activity (Jacobs et al. 1974, 1975a,b; Srebro and Lorens, 1975; Geyer et al. 1976; Costall et al. 1976), although in one study it was reported that the dorsal raphe lesion was more effective than the medial lesion in producing such actions (Przewlocka et al. 1977).

Lesions of the lateral mesencephalic raphe nuclei (B9) did not lead to any behavioural changes (Geyer et al. 1976). As has already been discussed, biochemical and other evidence indicates that the median nucleus projects to the hippocampus and other mesolimbic areas whereas the dorsal nucleus projects to the striatum and other forebrain areas (page 18). It has therefore been proposed that the locomotor effects of mesencephalic raphe lesions are mediated through the hippocampus.

Median or dorsal raphe lesions decrease the stereotypic effects of apomorphine and nomifensine (Costall et al 1975a; Costall and Naylor, 1977).

Intracerebroventricular injection or infusion of 5-HT has been found to cause a reduction in the spontaneous locomotor activity of rats (Green et al. 1976; Warbritton et al. 1978) and a reduction in the locomotor effects of amphetamine (Warbritton et al. 1978). Injection of 5-HT into the nucleus accumbens in rats has been reported either to have no behavioural effects (Jackson et al. 1975) or to cause a decrease in spontaneous locomotor and exploratory activity (Costall et al. 1976; Pijnenburg et al. 1976). The injection of 5-HT into the nucleus reversed in a dose-related manner the hyperactivity response to DA previously applied to the nucleus (Costall et al. 1976; Costall and Naylor, 1978). 5-HT receptor blockade by cyproheptadine reversed both this 5-HT inhibition as well as the inhibitory effects of neuroleptics on the DA response (Costall and Naylor, 1978). Finally, lesions of the median raphe nuclei potentiated the hyperactivity response to DA applied to the nucleus accumbens (Costall et al. 1976). In contrast to the findings of other workers (page 18) Costall et al. have reported their median raphe lesions to produce large reductions in the 5-HT content of cortex, striatum and "limbic forebrain". The last includes the accumbens nucleus and olfactory tubercle.

The behavioural syndrome (page 30) following treatment with 5-HT precursors in the presence of monoamine oxidase inhibitors or following 5-HT receptor stimulation is potentiated by selective degeneration of 5-HT neurones following intraventricular 5, 7-dihydroxytryptamine

administration (Trulson et al. 1971). It is not clear why 5-HT precursors should be effective in situations where the serotonergic neurones have been destroyed. Lesions of the striatum and serial transections as far as the posterior midbrain have no effect on the syndrome (Jacobs, 1976).

CONCLUSION

The drug studies point overwhelmingly to a powerful influence of dopaminergic systems in the regulation of exploratory, stereotyped and locomotor behaviours. Noradrenergic influences may also play a less important role in the mediation of locomotor and possibly exploratory behaviour. Serotonergic influences seem to exert antagonistic effects on locomotor behaviour but there is less evidence concerning such influences in the mediation of stereotyped behaviour.

Studies employing stereotactic lesions of monoamine pathways or stereotactic application of neurotransmitters and psychoactive drugs to specific brain areas further indicate that mesolimbic and nigrostriatal DA pathways exert differential effects on locomotor and stereotyped behaviours and that different systems are concerned with different forms of stereotypy. These studies have failed to show any important role of noradrenergic systems, but the studies of NA pathway manipulations are limited. Again there is some evidence of antagonistic influences of 5-HT systems on locomotor and exploratory behaviours.

When examining the roles of individual monoamine systems on behaviour, the functional interactions of the

three systems must always be remembered.

It is evident that much contradiction exists in the findings regarding the effects of manipulation of central monoamine systems on exploratory, stereotyped and locomotor behaviour, whether the manipulation be with systemically or locally applied drugs or with discrete lesioning. The majority of studies have involved examination of only one of the three behaviours, or at best, two. The studies presented in this thesis involve simultaneous quantitative examination of all three types of behaviours in an attempt to examine the relationships between these behaviours as well as the roles of monoamine systems in their regulation.

II. METHODS AND MATERIALS

Experiments reported in this thesis involved a study of rat behaviour under a variety of circumstances.

Exploratory, stereotyped and locomotor behaviours were monitored by a "hole-board" method. The effects of certain drugs administered systemically or intracerebrally on such behaviour have been studied. In some experiments rats with electrolytic or chemical lesions in selected brain areas were employed. Accuracy of location of intracerebral injections and of electrolytic lesions was determined histologically post mortem. Estimation of dopamine and noradrenaline in brain tissue was used to assess the degree of chemical lesioning and estimation of amphetamine in plasma and brain tissue were carried out on occasion.

The various methods are described in detail below.

1. ANIMALS AND THEIR MAINTENANCE

Male Wistar rats were used in all experiments. For 14-21 days before behavioural study, the animals were kept four to a cage in a room in which the light-darkness cycle had been artificially altered, the lights being switched on between 2000 hours and 0800 hours and darkness maintained between 0800 and 2000 hours. Food and water was supplied ad libitum. Just before behavioural study each animal was transferred singly in a small cage to the experimental room. For the acute drug studies and the studies of the effect of stereotactic intracerebral injection of monoamines each animal was used once only. Animals with stereotactic

lesions were studied on three occasions at intervals of one week, the first being 10-14 days after lesioning. Animals weighed 250 ± 20 g at time of experiments, except in certain experiments with stereotactically lesioned rats, where the weight at time of experiment was difficult to control.

2. PROCEDURE FOR MONITORING BEHAVIOUR FOLLOWING SPECIFIED PRETREATMENTS

The animal was placed in the middle of the floor of the hole-board apparatus described below. The door of the air-conditioned thermostatically-controlled compartment housing the hole-board apparatus was closed and automated quantitation of certain aspects of the animal's behaviour started immediately. Closed-circuit television allowed observation of the behavioural pattern without disturbance of the animal. During such observation behaviours such as head dipping into the holes of the hole-board, locomotor activity, grooming, rearing, immobility, sniffing and stereotyped behaviours were noted.

The Hole-Board Apparatus

The hole-board apparatus (Fig. 6) consisted of a square open field 35x35 cm with an aluminium floor. Evenly spaced on the floor were 16 holes 3.5 cm diameter arranged in four parallel rows of four holes each. The floor was supported 8 cm above a sturdy table surface. The field was surrounded by vertical perspex walls 22 cm high. A detachable perspex roof completed the box. Ventilation was provided by 21 air holes 0.5 cm diameter

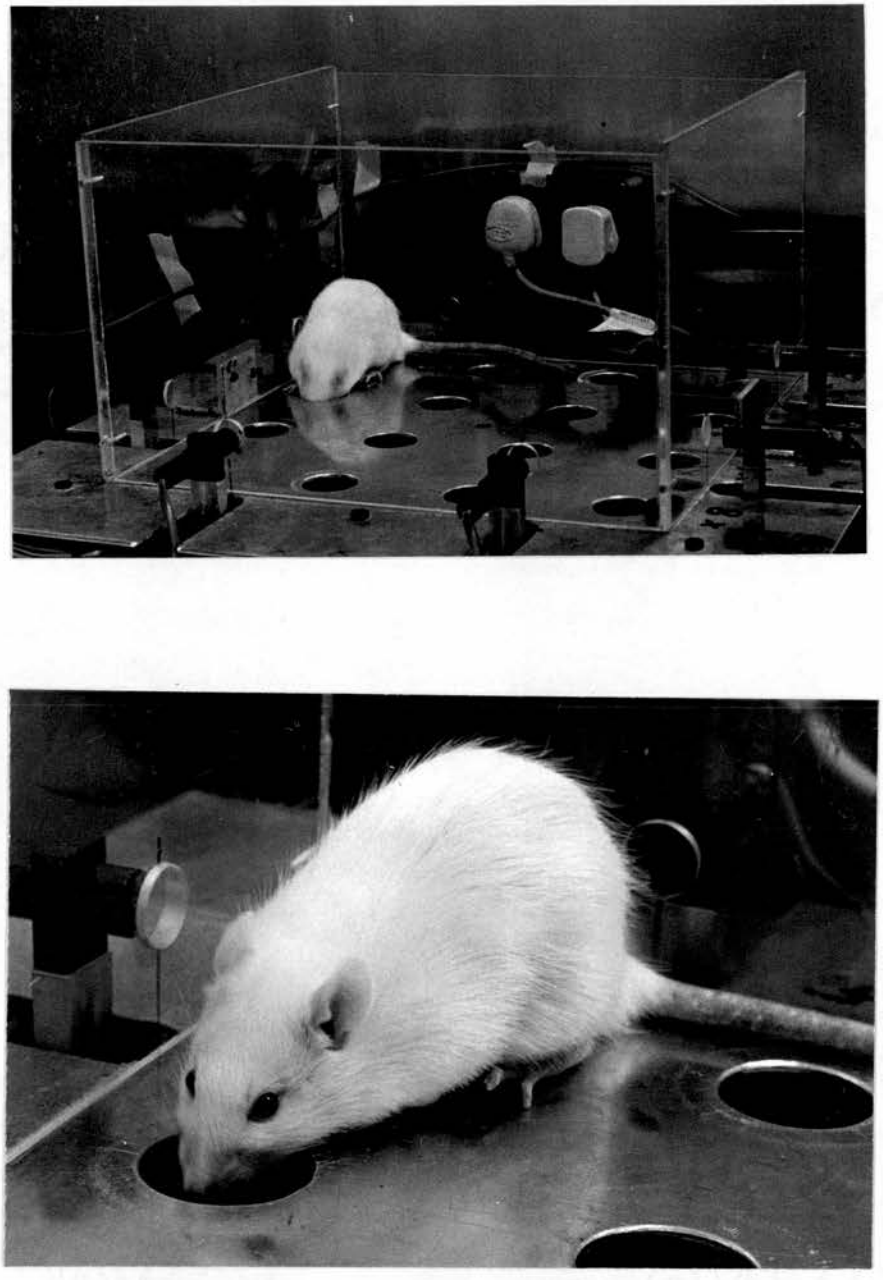


FIG. 6: The hole-board apparatus. A rat is seen dipping its head into a hole.

drilled in the roof and completed through the holes in the floor. A tissue-covered board was positioned under the floor during each experiment to collect faeces and urine for easy disposal. The apparatus was kept in an air-conditioned compartment 3 m high, 1.7 m long and 1.5 m wide on a sturdy table-top 1 m above the floor. The compartment was sound-proof and maintained at a temperature of 22 ± 1°C. Subdued lighting was provided by a 15 watt red light bulb. After each experiment the apparatus was cleaned with warm water.

A detection system was installed on the hole-board so that a record could be obtained of (a) the sequence of hole-dips performed by an animal on the board and (b) its locomotor activity, i.e. an estimate of how much the animal moved around on the hole-board. These behaviours were monitored using infra-red detectors and recorded on a teletype machine.

In order to monitor hole-dipping, eight infra-red transmitters were arranged beneath the sides of the hole-board so that two sets of four parallel beams each passed at right-angles to each other at a depth of 1.5 cm beneath the floor. The depth of the infra-red beams beneath the floor was such that they were interrupted when both eyes of the animal reached the level of the hole. Each beam passed beneath a row of four holes so that each hole had two beams passing through its centre at right-angles. Each hole was thus labelled according to which two beams passed beneath it (Fig. 7). Each beam was focussed onto an infra-red receiver on the other side of the hole-board.

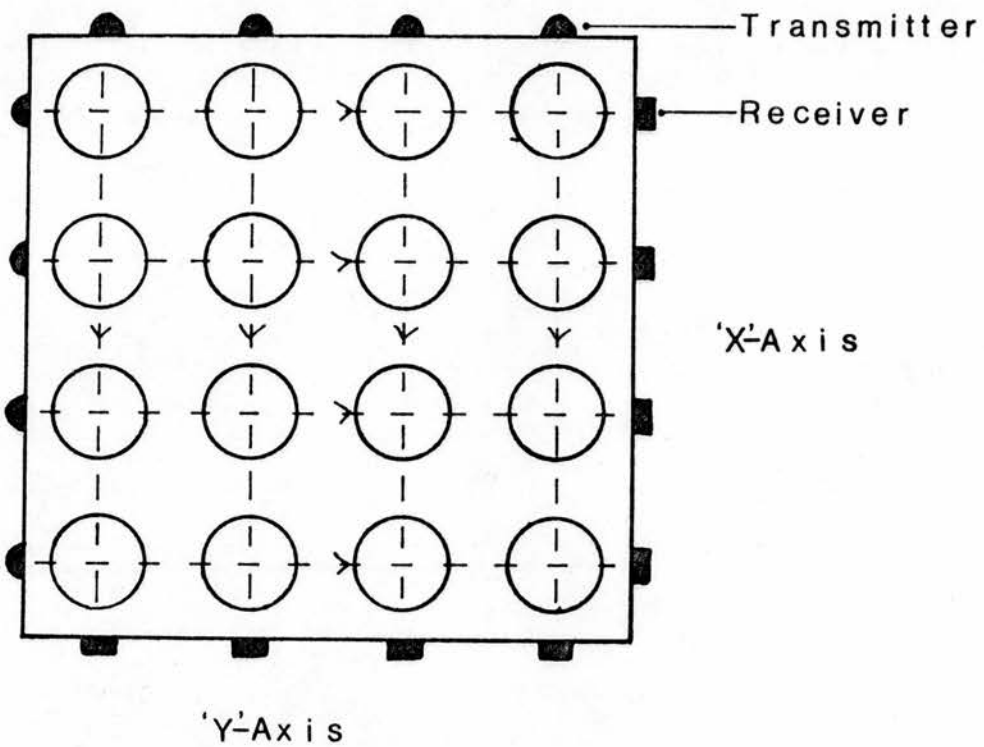


FIG. 7: The arrangement of the infra-red transmitters and receivers beneath the floor of the hole-board. Discontinuous lines represent the infra-red beams. Each combination of two intersecting beams is unique to one individual hole and thus effectively "labels" that hole.

When a rat dipped its head into a hole, the two beams that intersected that particular hole were interrupted, and this was detected by the two infra-red receivers onto which the beams were focussed. The infra-red transmitters and receivers were mounted on a sturdy base-plate of ¼" thick mild steel, accurately machined so that each device could be held rigidly in focus. The two axes on which the two sets of infra-red beams were arranged were designated the "X" and "Y" axes (Fig. 7).

Locomotor behaviour was monitored by four further sets of infra-red transmitters and receivers arranged on adjacent sides of the hole-board so that two pairs of parallel beams passed at right angles to each other 3.5 cm above the floor. The arrangement of these devices is depicted in Fig. 8. These overhead infra-red beams were broken as the animal moved around on the hole-board.

The output from each infra-red receiver was available as an electrical level which changed when the infra-red beam which was focussed onto it was broken.

The recording system for the holes is depicted in Fig. 9. The outputs from the four receivers on each axis passed onto a 4-input NAND gate used in OR function. The gate output fed into a bistable.

The eight detector outputs were also fed into a shift register so that they were available for transmission. When a gate output changed, the bistable was latched. When both bistables were latched the outputs were detected at a 2-Input AND Gate, which triggered a monostable. The monostable output loaded the shift register with the inform-

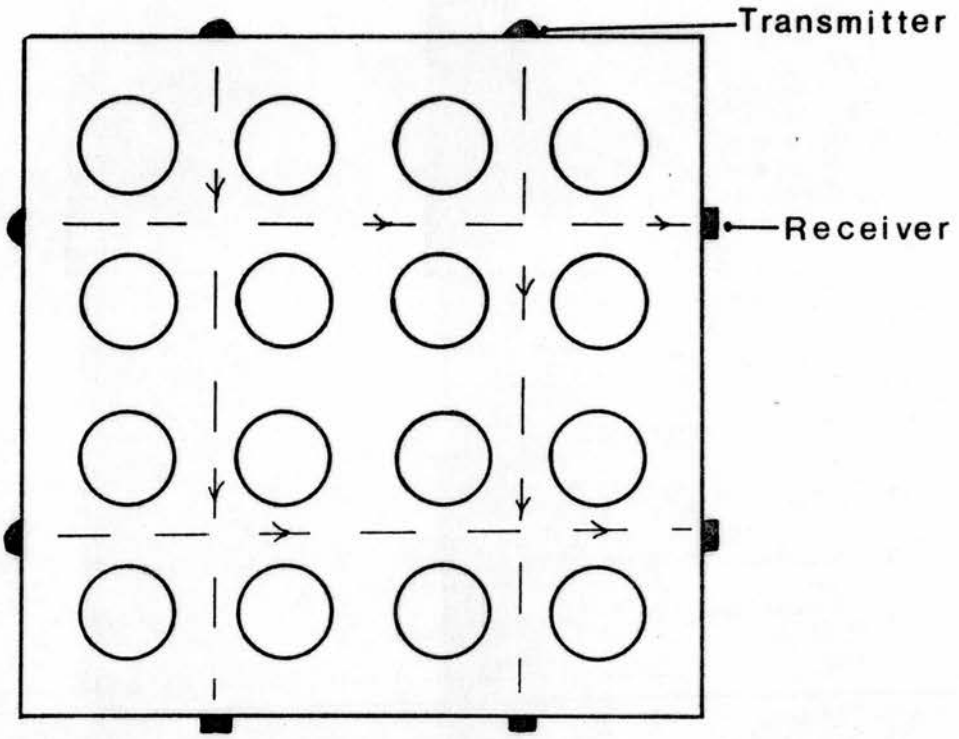


FIG. 8: The arrangement of the four infra-red receivers and transmitters above the hole-board floor for monitoring of locomotor activity. The infra-red beams (discontinuous lines) are interrupted as the animal moves around.

ation at X and Y axes, plus a pre-coded (ASCII) carriage return and line-feed signal and triggered the teletype clock generator. This generator clocked the shift register for the output device and provided pulses to the counter, which counted up to the required number of pulses for the total number of output characters. When the counter reached its maximum, a pulse was generated via a monostable. This reset both input bistables and the clock generator.

The outputs from the four infra-red receivers subserving the locomotor recording, fed through a 4-input OR gate into a monostable and thence into a counter (Fig.10). A timer was set to output every 10 minutes and load a shift register with the activity count and the time marker character "X". A character shifting circuit similar to the one described for the hole-dips was used to output this information to the teletype and afterwards reset the activity counter and timer. The hole-dip circuit was inhibited when the time marker output was operative.

The teletype produced a printed plus a punched paper-tape output. The printed output consisted of a column of pairs of numerals representing hole-dips, one for each hole-board axis. Every ten minutes a time-marker character "X" was printed, followed by a five digit number representing the number of recorded interruptions of overhead beams during the preceding ten minutes i.e. the "locomotor activity count". The punched paper-tape output was employed in computer analysis of the records.

It would have been preferable to record each

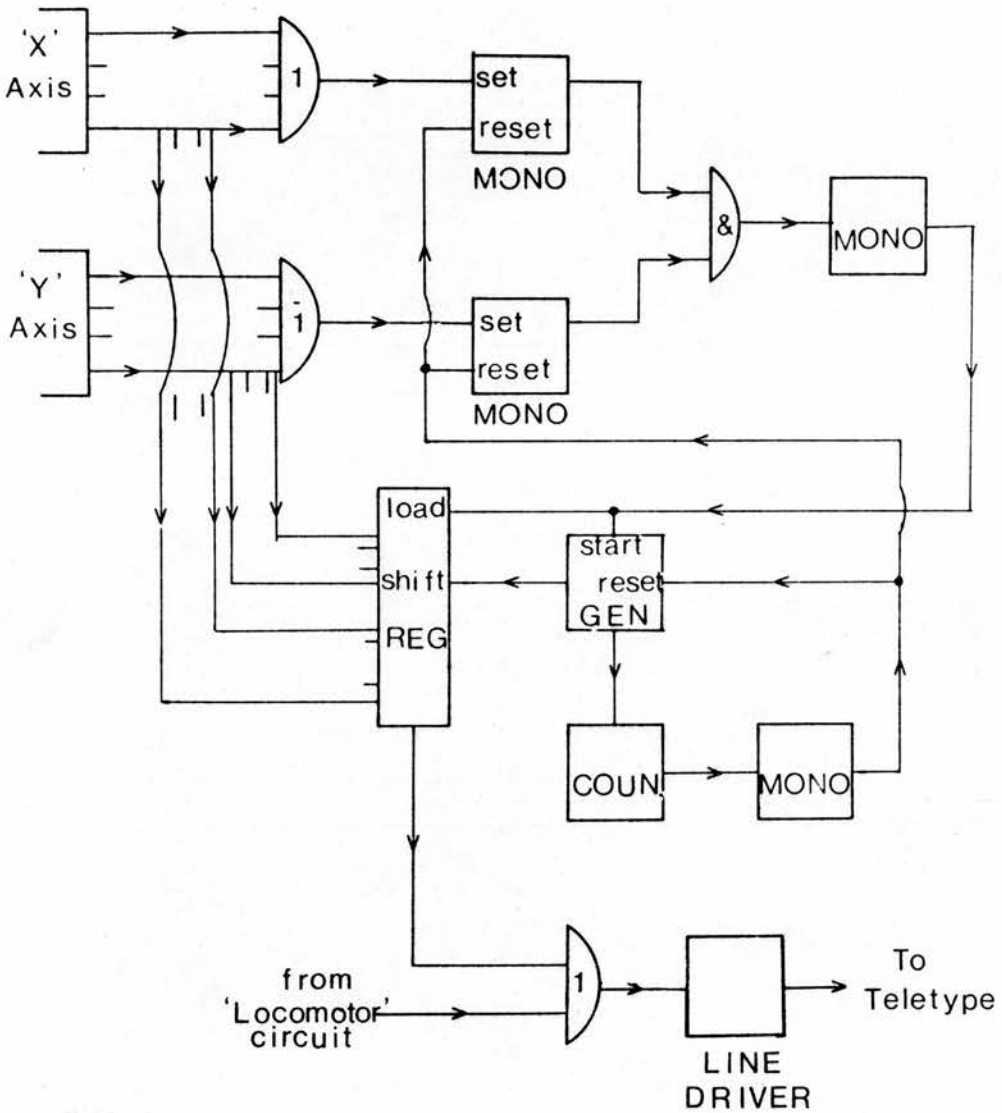


FIG. 9: Flow diagram of the circuit employed for monitoring hole-dipping detected in the hole-board apparatus.

MONO - Monostable
REG - Shift register
COUN - Counter
GEN - Clock generator
& - AND Gate
1 - OR Gate

interruption of a locomotor beam as it occurred. This would have allowed differentiation of repetitive interruptions of the same infra-red beam from successive interruptions of different beams which would represent true locomotor activity. Unfortunately the teletype employed for the recording could handle only one event every 400 milliseconds. If it had been attempted to record both hole-dips and locomotor beam interruptions as they occurred, many of these events would have occurred during the 400 m. sec. period that another event was being recorded by the teletype, particularly if an animal was indulging in a high level of both hole-dipping and locomotion. An alternative solution would have been to employ a separate teletype for the recording of locomotor activity.

Because the infra-red receivers subserving the overhead beams fed into an OR gate, there was the situation that any beam interruption could be recorded only when every other locomotor beam was intact. This being so there would be a tendency for a reduction in the counts of repetitive beam interruptions under the influence of up and down or to and fro movements of some part of the animal's body since when this occurred some other stationary part of the body was usually interrupting another beam. However when the animal moved about different overhead beams were continually being successively interrupted and disinterrupted, so that a continuing registering of locomotor activity was obtained.

A major problem with the apparatus was caused by the fact that it was not possible to obtain proper earthing of

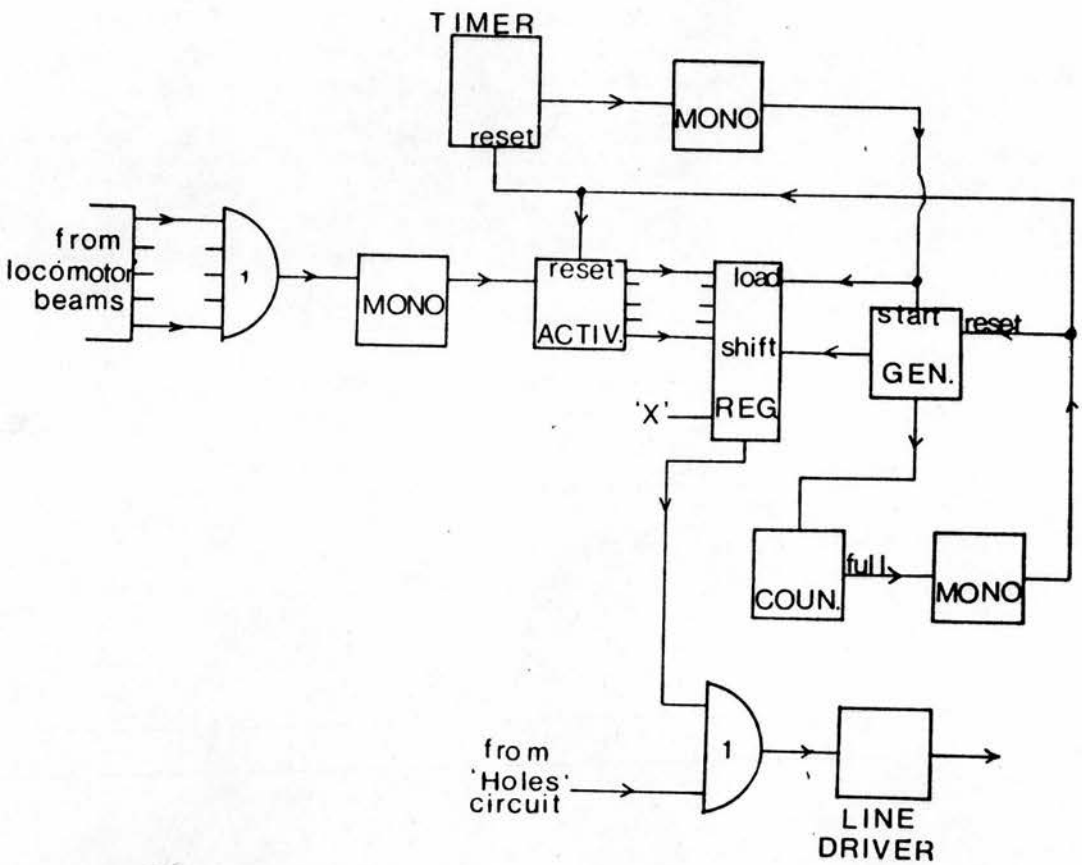


FIG. 10: Flow diagram of the circuit employed for monitoring locomotor counts from the hole-board apparatus as well as the time-marker facility.

MONO - Monostable
REG - Shift Register
COUN - Counter
GEN - Clock Generator
ACTIV - Activity Counter
1 - OR Gate

the electrical supply in the building. There was therefor a possibility of a high degree of intermittent electrical interference which sometimes confounded the recordings. Such interference would cause an immediate record of "? ?" on the teletype in the sequence of numerical characters representing the hole-dips. That in itself was no problem, since such an obviously spurious entry could be excluded from the analysis of the results. More importantly, the electrical interference sometimes affected the locomotor activity counter, leading to a spuriously high measure of activity during that 10 minute interval. Such items on the record were again easily recognisable since they invariably appeared as counts of several thousand or more. Such entries were rejected from the analysis, the criterion for rejection being that of a locomotor activity count of 1000 or more which was also over ten times that of the preceding and succeeding counts. The occasional incomplete locomotor activity record because of this was unavoidable. The problem was greatly minimised after the apparatus was connected to a different phase of the electrical supply and all other electrical equipment disconnected from that phase.

Another source of spurious counts for hole-dipping was the intrusion of the feet and occasionally the tail of the animal into holes. Such a protrusion was normally recorded as a hole dip. At other times a limb or tail intrusion coincided with a head dip into another hole in which case the numerical characters recorded did not correspond to any of the numbers by which individual holes

were identified, the numerals recorded being a summation of the codes on each axis for the two sets of beams interrupted. During analysis of the records, spurious entries were noted as errors and rejected. It follows that these errors would tend to occur more frequently when the animal was moving around. In general such "errors" amounted to less than 3% of the total number of recorded hole-dips.

Analysis of the Records for Hole-Dipping and Locomotor Activity

The rationale for the method of differentiating exploratory from stereotyped behavioural patterns has been previously described (Makanjuola, 1976: Makanjuola et al. 1977a). The following operational definitions were used. An "exploratory dip" was defined as any head-dip into a hole different from the previous one. A "stereotyped dip", on the other hand, was a dip which occurred into the same hole as the previous dip. In other words, if a rat dipped in the following hole sequence (each two-digit number coding for a particular hole) - 11, 18, 42, 42, 11, 44, 14, 14, 14, 28, a total of seven "exploratory dips" and three "stereotyped" dips had occurred. The contribution of "stereotyped" dipping to the dipping activity is given by the ratio of "stereotyped" dips to the total number of exploratory plus stereotyped dips during any period of time (The "S/T ratio").

The punched tape record from the teletype for each experiment was analysed by a GEC 905 computer. The numbersof "stereotyped" dips, "exploratory" dips,

total dips, the S/T ratio and locomotor activity counts were computed for each 10 minute and 30 minute interval as well as for the entire period of each experiment.

Statistical Treatment of Results

Non-parametric statistical methods were used throughout. When groups of three or more results were evaluated, a Kruskal-Wallis one-way analysis of variance was used (Siegel, 1956). With two groups of results a Mann-Whitney U test was used, significance levels being those for a 2-tailed "t" test (Siegel, 1956). Results were regarded as being statistically significant if the probability of the differences occurring by chance was less than 0.05%.

3. DRUG TREATMENTS

Systemic administration. All systemically administered drugs were injected intraperitoneally (i.p.) in a volume not more than 2 ml/kg body weight. Drug doses are given in terms of the appropriate salt. With three exceptions, drugs were prepared for injection by dissolution in physiological saline. Phenoxybenzamine hydrochloride was dissolved in a minimal quantity of glacial acetic acid and made up to the required volume with saline. Haloperidol was prepared for injection by dilution of the commercial preparation for injection with saline. Apomorphine hydrochloride solution (Evans Medical) was administered undiluted.

Intracerebral injections. NA and DA (as the hydrochlorides) and 5-HT (as the bimaleinate) were injected intracerebrally into conscious animals. 6-Hydroxydopamine was injected intracerebrally to achieve chemical lesioning of DA terminals. The procedures are dealt with in detail in the appropriate section.

4. ELECTROLYTIC AND CHEMICAL LESIONING OF SELECTED BRAIN AREAS. IMPLANTATION OF PERMANENT GUIDE CANNULAE FOR INTRACEREBRAL INJECTION.

These procedures were carried out under stereotactic control.

Stereotactic Procedures

The initial stages of all stereotactic operations were identical in all three procedures. Male Wistar rats weighing 155 ± 5 g at the time of operation were used. The animal was anaesthetized with a halothane/medical air mixture using a "Mini-Boyle" anaesthetic apparatus (B.O.C.). Gas flow rate was 2.0 litres/minute. Induction was achieved using a halothane concentration of 5% and anaesthesia maintained with a 2-3% concentration. The animal was then secured in a Kopf stereotactic frame on which the jaw bar was set at -2.5 mm. The ear bars used were those designed for use in guinea-pigs, which had blunter ends than those designed for rats and were therefore less traumatic. The scalp was shaved with electric clippers and the skin cleaned with tincture of iodine followed by absolute alcohol. A mid-line incision was made starting about 1 cm anterior to the bregma and ending a short distance behind the lambda (Fig.11). The two scalp flaps were then separated and the periosteum rubbed off with gauze. Where necessary a retractor was used to improve exposure of the operation field.

All coordinates used were with reference to the bregma (antero-posterior (A-P) and lateral coordinates) and the dorsal cortical surface (vertical coordinates).

The coordinates used originally were derived from the stereotactic atlas of König and Klippel (1963). Preliminary experiments showed that these coordinates did not relate accurately to the brain areas aimed at and they had to be modified. The final coordinates arrived at(in mm.) were asfollows: The nucleus accumbens; A-P + 1.6, Lateral ± 1.5, Vertical - 7.0. The caudate-putamen; A-P + 0.5, Lateral ± 2.7, Vertical - 4.5.

Electrolytic lesions of the nucleus accumbens

A variable current DC power supply was constructed for inducing the electrolytic lesions. The current was applied through an entomoligical pin, 0.35 mm diameter, insulated except at its terminal ½ mm. with "INSL-X" insulating compound. The electrode was secured on the electrode carrier in a vertical position and carefully adjusted so that it was exactly vertical. The electrode tip was lined up on the bregma and the required antero-posterior and lateral coordinates determined from the readings on the frame. Two holes 1.7 mm diameter were made in the skull on either side of the sagittal suture over the proposed lesion sites using a "Renda" dental drill with a No. 6 round burr (ASH). The electrode, which had been positioned at the antero-posterior and lateral coordinates for the target area was then lowered the required depth from the cortical surface. The neutral electrode, a crocodile clip, was connected to the skin flap. A current of 2 mA was passed for 15-30 seconds on each side to induce the lesion, and the electrodes

removed. For "sham" lesions the electrode was lowered to a vertical coordinate just above the target organ, and no current was passed. The wound was cleaned, sprayed with "Polybactrin" antibiotic spray and the scalp incision sutured.

Chemical lesioning of the dopaminergic terminals of the caudate-putamen and nucleus accumbens by intracerebral injection of 6-hydroxydopamine (6-OHDA). (Fig.12)

Thirty minutes before the 6-hydroxydopamine injection each animal was pretreated with desmethylimpramine hydrochloride 25 mg/kg to minimise destruction of NA terminals (see page 42) and pargyline hydrochloride 50 mg/kg to potentiate the effects of the 6-OHDA (Iversen and Kelly, 1975).

An "Agla" micrometer syringe mounted on an Agla micrometer injection unit (Wellcome Reagents) was used to administer measured amounts of 6-OHDA through a "Portex" polythene'intravenous'cannula which terminated on a 0.3 mm diameter dental needle. The needle was mounted on the electrode carrier in a vertical position so that the bevel faced caudally for nucleus accumbens injections and rostrally for caudate-putamen injections. The needle was aligned at the desired coordinates by the same procedure as used in the induction of electrolytic lesions of the accumbens nuclei.

6-hydroxydopamine hydrobromide was prepared for intracerebral injection by dissolving 4 mg (as the base) in 1.0 ml chilled physiological saline. L-ascorbic acid 2 mg/ml was added as antoxidant. During preliminary

experiments, the dosages of 6-OHDA required to produce effective DA depletion in the two nuclei were determined. For nucleus accumbens lesions, 20 µg 6-OHDA in 5 µl saline were injected on each side. Neostriatal lesions were achieved with 24 µg 6-OHDA in 6 µl saline on each side. The 6-OHDA was infused at the rate of 1 µl per 30 seconds. "Sham" lesions were made by injection of 2 µl physiological saline in each side. The scalp wound was cleaned where necessary, sprayed with "Polybactrin" and then sutured.

Experiments on operated animals

Animals operated on for the production of lesions or insertion of guide cannulae were used for further experimentation after a lapse of 12-14 days.

Intracerebral Injections of Monoamine Transmitters into Conscious Animals

These injections were made through permanent guide cannulae implanted at a previous operation under stereotactic control.

(a) Implantation of guide cannulae for injection of monoamine transmitters into the nucleus accumbens and caudate-putamen (Fig. 13).

The guide-cannulae were made from stainless steel screws 6.0 mm long, 3.0 mm diameter designed for chronic recording of electrocorticograms in rats (Fig.14). These screws were already patent through the upper half. That channel was made completely patent by drilling a hole through to the bottom exactly 0.51 mm diameter into which the injection needle would fit snugly.

FIG. 11: Early stages of a stereotactic operation. The skull has been exposed and holes drilled bilaterally over the proposed lesion sites or in the positions for insertion of guide cannulae.

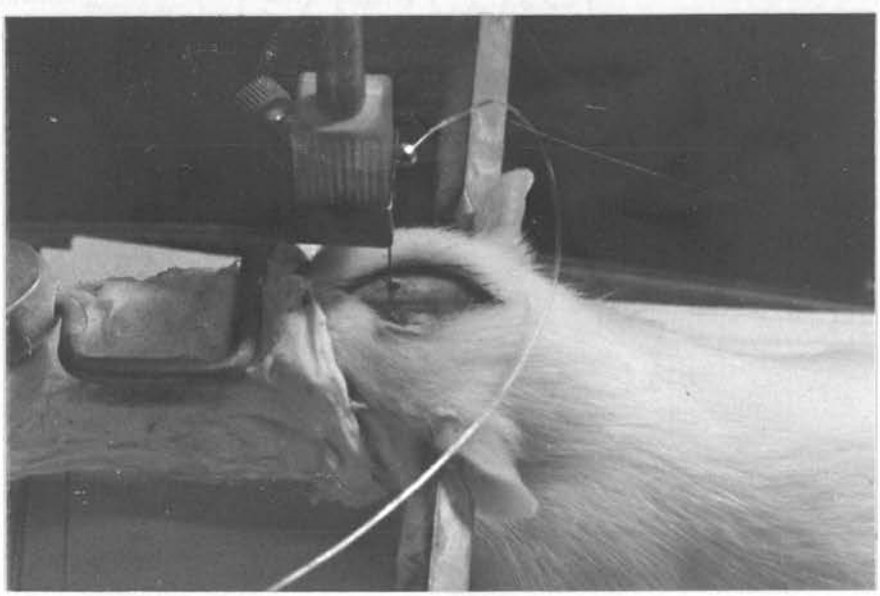
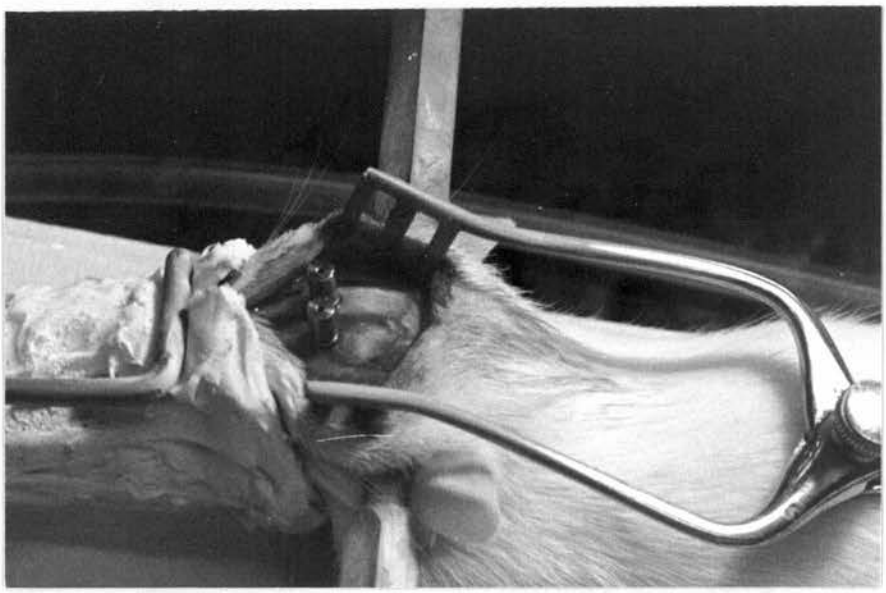


FIG. 12: Stereotactically-controlled injection of 6-hydroxydopamine into the caudate-putamen.

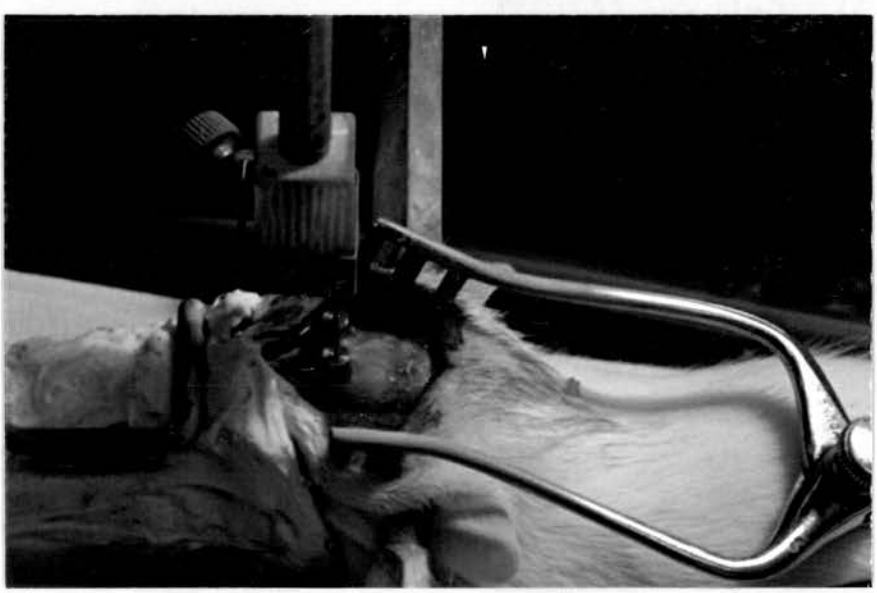
A 75 gauge drill (0.51 mm diameter) was mounted vertically on the electrode carrier to serve as a guide for exact placement of the guide-cannulae. Using a No. 6 burr, two holes 1.65 mm diameter were drilled in the skull with their centres at the exact desired antero-posterior and lateral coordinates with reference to the bregma.(page 64) The guide cannulae were screwed in with the aid of specially modified straight artery forceps. On each side in turn, the guide drill mounted on the electrode carrier, set at the exact antero-posterior and lateral coordinates for the target organ, was lowered into the cannula to hold it in exact position while it was permanently secured with acrylic dental cement. The exposed skull wound was cleaned and sprayed with "Polybactrin". With cannulae inserted for n. accumbens injections, which were close together on either side of the mid-line, a triangular piece was cut from each side of the incised skin so that the edges of the scalp wound could be brought together around the two cannulae and sutured. With cannulae aimed at the caudate-putamen areas, which were further apart, a hole was made in the skin on each side over the positions of the cannulae. The edges of the scalp incision could then be repaired with the cannulae protruding through the two holes.

(b) <u>Intracerebral injection of monoamine transmitters into conscious animals</u>.

Animals were pretreated with nialamide ("Niamid") 100 mg/kg i.p. 2 hours before intracerebral injection.



a



b

FIG. 13: Insertion of guide cannulae for later injection of monoamines into the caudate-putamen nuclei in conscious animals; (a) the cannulae have been inserted into the skull, (b) the cannulae have been fixed with acrylic dental cement.

Intracerebral injections were performed using an "Agla" micrometer syringe and injection unit attached to a 25 G. "Yale microlance" disposable needle which had been shortened to protrude exactly the desired depth from the bottom of the guide cannulae situated at the cortical surface. With reference to the mid-point of the bevel of the needle this distance was 6.5 mm for nucleus accumbens injections and 4.5 mm for caudate-putamen injections.

The animal was restrained and the injection needle inserted into the guide cannula, which had previously been cleared, if necessary, of dried clotted protein and blood with a specially shortened 25G Yale needle or with a No.75 drill bit. The required dose of monoamine (as the respective salt) was then injected into each side in 1 µl saline over a 10 second period, followed by a 10 second pause before removal of the needle. The animal was then placed in the hole-board apparatus and behavioural recording started immediately.

5. HISTOLOGY

Staining of Tissues

Histological examination of injection tracks and electrolytic lesions of rat brain were performed using the Luxol Fast Blue/Cresyl Echt violet staining method (Kluver and Barrera, 1953). Animals were deeply anaesthetized with 0.5 ml of 20% (w/v) solution of chloral hydrate i.p., decapitated and the brain removed. The brain was transected vertically at the mid-hypothalamic position and the anterior portion frozen with a jet of carbon dioxide gas. Sections

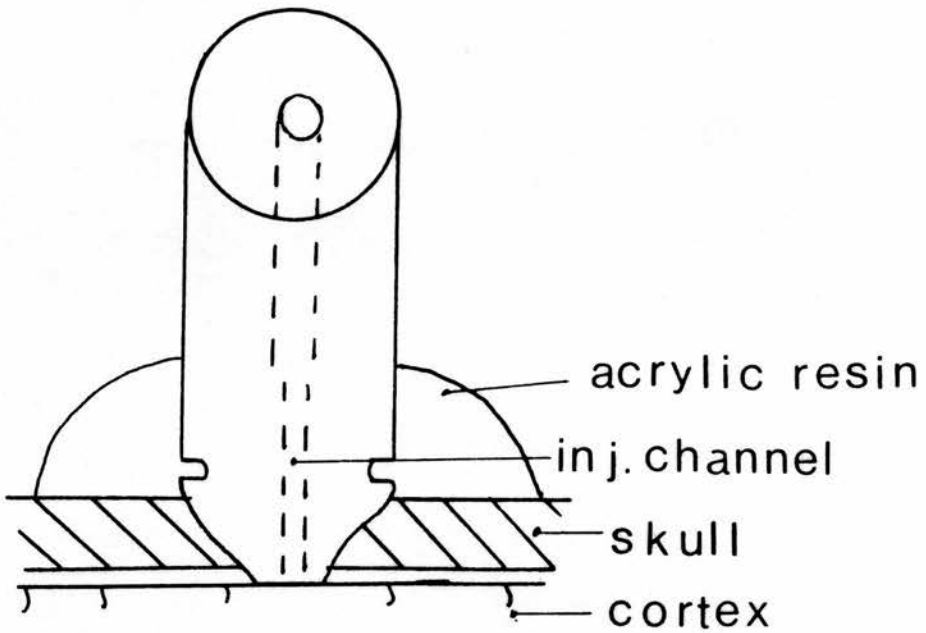


FIG. 14: Diagram of the guide-cannulae implanted into the skull for later stereotactically-controlled injection of monoamines or saline into discrete brain areas. The guide-cannulae are made of stainless steel and measure 6.0 mm long and 3.0 mm diameter. They are held firmly in position in the skull with acrylic dental cement.

of 20-40 μm thickness starting anterior to the target area were cut in a Linde Kryostat at -25°C and collected onto microscope slides and stored in 70% (v/v) alcohol before staining.

The following materials were employed: 0.1% Luxol Fast Blue (British Drug Houses) in 95% alcohol to each litre of which was added 5 ml 10% (v/v) acetic acid; 0.1% Cresyl echt violet (Fluka AG) in distilled water to which was added 2 ml 10% (v/v) acetic acid per 350 ml; 0.05% lithium carbonate in distilled water; 100% alcohol (James Borrough), 95% (v/v) and 70% (v/v) alcohol; Xylene (British Drug Houses); Depex mounting medium (Gurr). Luxol Fast Blue could be made in quantity and stored. The Cresyl echt violet solution was made up fresh and filtered before use.

The sections were transferred from storage in 70% alcohol into 95% alcohol for 1 min. and then stained for 15 min. in Luxol Fast Blue solution. Excess stain was removed by repeated immersion in 95% alcohol and then the sections washed by immersion in distilled water. Differentiation was carried out by a quick immersion in 0.05% lithium carbonate followed by repeated immersion in 70% alcohol and then in distilled water. This lithium carbonate-alcohol-water sequence was repeated 2-3 times until satisfactory differentiation of white matter from grey matter was obtained, the white matter being stained greenish blue. The sections were counterstained for 8 min. in cresyl echt violet solution at 40 ± 5°C. Differentiation of the cresyl violet stain was achieved

by subsequent repeated immersion in 95% alcohol. The tissue sections were dehydrated by immersion in absolute alcohol for 1 min, cleared in xylene and mounted with Depex mounting medium. The Luxol Fast Blue stained the white matter greenish blue while the cresyl echt violet stained cell bodies violet.

Assessment of Electrolytic Lesions and Injection Tracks

A standard sheet (Fig. 50) of scale drawings of serial transverse sections of the rat brain was prepared. Each drawing obtained was an appropriately reduced photograph of outlines traced from drawings of sections of the rat brain in a stereotactic atlas (König and Klippel, 1963). The drawings represent serial sections from antero-posterior coordinates of 7.470 mm to 11.050 mm inclusive i.e. from the position of the bregma to a point 2.5 mm anteriorly.

When serial sections from the brains of each rat were examined the histological changes observed were represented on the drawing of the corresponding section on the standard sheet. In this way the position and extent of electrolytic lesions could be assessed, as well as the position of needle tracks and any other accompanying histological changes. The extent of electrolytic lesions was expressed as a percentage of the entire target organ, taking into account the degree of damage visualized on each section.

6. BIOCHEMICAL ESTIMATIONS

Estimation of Dopamine and Noradrenaline in Brain Tissue

The method was that of Coyle and Henry (1973). The catecholamines are converted to their 3-O-[^{3}H] methylated derivatives by reaction with [^{3}H-methyl] S-adenosylmethionine (SAM) in the presence of catechol-O-methyl transferase. The [^{3}H] methyl derivatives are then separated by solvent partitioning following oxidative cleavage of the side chain of the noradrenaline derivative at the β-hydroxyl group with sodium metaperiodate to give [^{3}H-methyl] vanillin, 4-hydroxy, 3- methoxybenzaldehyde.

(a) Dissection of Tissues

The rats were killed by a blow on the back of the thorax and decapitated. The brain was quickly removed and dissected on a glass plate resting on crushed ice. Samples were immediately transferred into liquid nitrogen and stored therein until homogenisation. The dissection followed the guidelines given by Horn et al. (1974). With the brain lying ventral surface up, the two olfactory tubercles were first removed with the aid of curved watch-makers' forceps. Then, with the aid of two razor blades a coronal cut was made 2½ mm anterior to the anterior border of the optic chiasma(Fig. 15a). A second cut was then made at the anterior border of the optic chiasma, to produce a slice of tissue 2½ mm thick (Fig. 15b). This brain slice was then laid flat caudal surface upwards and a cut made passing through the ventral tips of the lateral ventricles. A rectangular block containing the two

accumbens nuclei was then separated from the ventral part of the tissue by making vertical cuts passing just lateral to the anterior commisures (Fig. 15b). The caudate-putamen areas were separated from the rest of the dorsal piece of tissue by blunt dissection using a microspatula. A sample of cortical grey matter was also obtained from the lateral and dorsal surfaces of the remaining tissue by careful cutting with a razorblade. To allow rapid dissection and reproducibility, no attempt was made to obtain the posterior portion of the caudate-putamen.

The pieces of tissue obtained were weighed frozen just before the start of the assay. Mean weights (mg) ± Standard deviation from samples obtained from all the rats were as follows:

Olfactory Tubercles :	11.5 ± 2.0
Nucleus Assumbens samples :	24.1 ± 5.0
Caudate-putamen samples :	27.0 ± 5.3
Cortical grey matter samples:	70.0 ± 13.2

(b) Estimation of the catecholamines

Tissues were homogenized with ice-cold 0.1M perchloric acid (PCA) in a 2 ml glass homogenisation tube using a Teflon homogeniser (Camlab). 300 µl 0.1M PCA was used for each 12.5 mg of samples of olfactory tubercles, accumbens nuclei and caudate-putamen areas and 300 µl for each 50 mg of cortex. Tissue extracts for making up standards and blanks were prepared from whole brain using 300 µl 0.1M PCA for each 12.5 or 50 mg of tissue. To remove precipitated protein and cell debris, homogenates

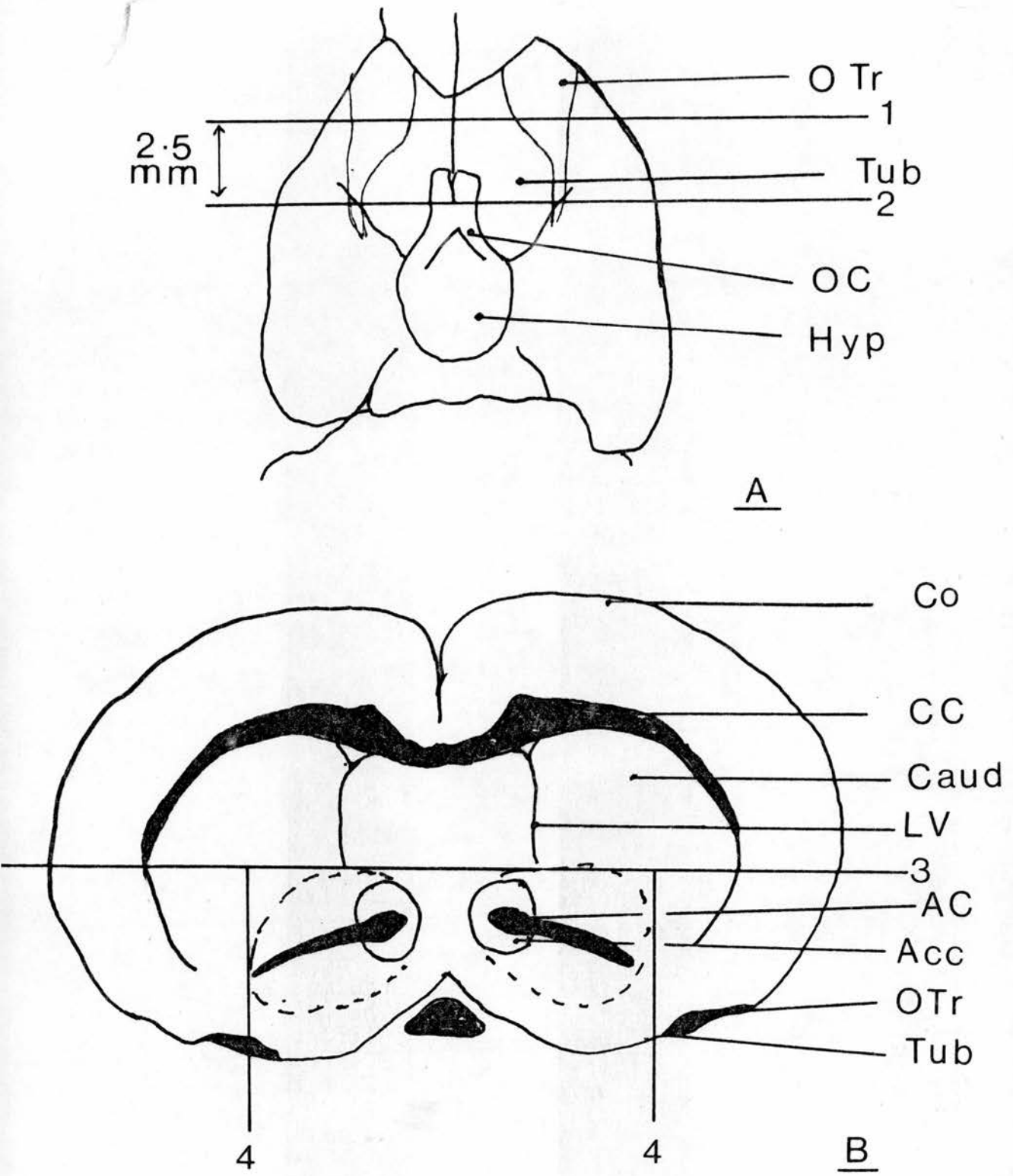


FIG.15: Method for dissection of different brain areas (p.71). A - ventral surface of rat brain showing location of the first two cuts (1 and 2); B - caudal surface of the slice of brain tissue thus obtained, showing the position of the cuts required for separation of the accumbens nucleus sample (3 and 4). Dotted lines indicate position of accumbens nucleus. OTr - Lateral olfactory tracks; Tub - olfactory tubercle; OC - optic chiasma; Hyp - hypothalamus; CC - corpus callosum; Caud - caudate-putamen; LV - Lateral ventricle; Acc - accumbens nucleus; AC - Anterior commissure.

of small volume were centrifuged in an Eppendorf 3200 centrifuge at 15,000 g for 5 min., while tissue extracts prepared from whole brain with a volume too large to be accommodated in this centrifuge were centrifuged in an MSE Mistral 22 at 10,000 g for 15 min.

300 µl of supernatant from each sample was placed in a 15 ml glass conical test tube. Where possible assays were performed on each sample in duplicate. Routinely, in addition to the tissues to be assayed, DA and NA standards were also assayed in duplicate using 300 µl whole brain homogenate to which was added 25 ng DA or 25 ng NA (as the base). These were assayed in parallel with duplicate portions of the same homogenate with no added amines. "Tissue blanks" were obtained by processing two further 300 µl portions of whole brain supernatant through the assay procedure but with the O-methylation step inhibited (see below). Two 300 µl portions of 0.1M PCA were used for duplicate reagent blank estimations.

To each tube was added 100 µl of a mixture containing:

500 µg dithiothreitol

0.5 µmol $MgCl_2$ (10 µl of a 10.165 mg $MgCl_2 6H_2O$/ml solution)

140 m.mol."TRIS" buffer at pH 9.6 (40 µl of a 424 mg "TRIS"/ml solution

25 µl Catechol-O-methyl transferase preparation

25 µl S-Adenosyl-L-[^{3}H-methyl] methionine (10x dilution of a stock preparation containing 9.2 - 12.6 Ci/mmol.)

The samples were then incubated at 37°C for 60 min.

before the reaction was ended by addition of 500 µl 0.5M borate buffer pH 10.0 and transfer to an ice-bath. The "tissue blank" tubes had 0.5 ml of the borate buffer added prior to the incubation mixture and remained in an ice-bath instead of being incubated.

(c) Extraction of methylated Dopamine and Noradrenaline

Carrier amounts of non-radioactive 3-methoxytyramine (7 µg), metanephrine (3 µg) and normetanephrine (3 µg) were added as a mixture of the hydrochlorides in 50 µl aqueous solution which also contained 1 mg ethylene diamine tetracetic acid as the sodium salt. O-methylated amines were extracted into 9.5 ml water-saturated ethyl acetate/ methanol mixture (10/1 by volume) which was added to the contents of each tube, following which the tubes were stoppered and shaken manually vigorously for 2 minutes. The tubes were then centrifuged at 2000 g for 5 minutes in an MSE Mistral II centrifuge and 8.5 ml of the upper organic phase transferred to a fresh tube containing 500 µl 0.5M borate buffer pH 10.0. These tubes were then stoppered and shaken for 2 min. and centrifuged at 2000g for 5 min. A 7.5 ml portion of the buffer-washed organic phase was transferred to a fresh test tube containing 500 µl of 0.1M hydrochloric acid and shaken for 2 min. in order to back extract the O-methylated catecholamines into an aqueous phase. The tubes were then centrifuged for 5 min. at 2000g before the upper organic layer was aspirated off. The aqueous phase was washed by shaking with 8 ml water-saturated ethyl acetate

for 2 min.; the phase was separated by centrifuging at 2,000 g and the ethyl acetate layer aspirated off.

(d) Oxidation of the metanephrines to vanillin

Sodium phosphate buffer, 500 µl 0.5M pH 7.5, was added to the washed aqueous extract and the tubes transferred to an ice-bath. To each tube was added 50 µl 3% (w/v) sodium metaperiodate, the solution mixed and the reaction allowed to continue in the ice-bath before being terminated after exactly 3 min. by the addition, with mixing, of 50 µl 10% (v/v) glycerol.

(e) Separation of the vanillin derived from the metanephrines from the 3-methoxytyramine

The vanillin derived from the periodate oxidation of the metanephrines was extracted by shaking of the solution with 9.5 ml toluene for 2 min. followed by centrifugation for 5 min. at 2000 g. The vanillin was now in the toluene phase while the 3-methoxytyramine was retained in the aqueous phase. The two phases were separately treated as follows:

(i) Measurement of [^{3}H-methyl] vanillin. The vanillin in a 9.0 ml portion of the toluene extract was back extracted into 1000 µl 1M sodium hydroxide by shaking for 2 min. and centrifuging. The organic phase separated by centrifugation was aspirated and discarded. The aqueous phase was acidified by addition of 100 µl glacial acetic acid and the vanillin re-extracted into 9.5 ml toluene by shaking and centrifuging. A 9.0 ml portion of the toluene extract containing the [^{3}H-methyl] vanillin derived from the

3-O-[^{3}H]-metanephrines was added to a 20 ml scintillation vial containing 400 µl "Liquifluor" scintillant. Each vial was counted for 1 min. in a Nuclear Chicago Mark II scintillation counter. Duplicate mixtures of 400 µl Liquifluor and 9.0 ml toluene were also counted to provide background counts.

(ii) Measurement of [^{3}H-methyl] 3-methoxytyramine. Following the removal of the toluene phase after the meta-periodate reaction and toluene extraction of the vanillin, the aqueous phase containing the [^{3}H-methyl] -3-methoxy-tyramine was washed with 5.0 ml toluene by shaking and centrifuging. After removal of the toluene by aspiration, 500 µl 1M borate buffer pH 11 was added to the aqueous phase and the O-methylated dopamine extracted into 5.5 ml of a toluene/isoamyl alcohol mixture (3/2 by vol.) by shaking and centrifugation. A 5.0 ml portion of the toluene/isoamyl alcohol extract was added to a 20 ml scintillation vial and mixed with 10 ml "NE 260" scintillant. Each vial was counted for 1 min. Background counts were obtained in duplicate from measurements of a mixture of 10 ml scintillant and 5.0 ml toluene/isoamyl alcohol mixture.

A ^{133}Ba external standard was employed during scintillation counting. Disintegrations per minute (d.p.m.) could then be computed from the counts per minute (c.p.m.) using the samples channel ratio method with the aid of an Olivetti P602 Programmer with LN 20 teletype tape reader.

Estimation of Amphetamine in Plasma and Brain Tissue

The method of Ånggard et al. (1970) was employed. The amphetamine after suitable extraction is estimated by gas chromatography, using an electron capture detector, of its trichloroacetyl derivative 1-phenyl-2-(trichloroacetamido) propane.

Animals were killed by a sharp blow on the head followed by decapitation. Freely flowing blood from the trunk was collected in a 5 ml capacity perspex tube containing pre-added potassium EDTA ("Greyward") to which a drop of physiological saline had been added 10 min. before to facilitate dissolution of the EDTA. The brains were then quickly removed and placed in liquid nitrogen, in which they were stored until analysed. A portion of each blood sample in a 1.5 ml "Eppendorf" plastic centrifuge tube was centrifuged in an Eppendorf 3200 centrifuge at 15000g for 3 min. to obtain the plasma, which was transferred to a fresh tube and stored overnight in a deep freeze at - 28°C prior to analysis.

Throughout the assay method all test-tubes used had been siliconised using "Sigmacote" siliconizing fluid.(Sigma). This was in order to prevent the adsorption of the assay products onto the glass. The toluene used was of the "special for chromatography" grade (B.D.H.).

(a) Estimation of Amphetamine in Plasma

To 500 µl plasma in a siliconized glass 15 ml conical test tube was added 1000 µl distilled deionized water and 50 µl 5M sodium hydroxide. The amphetamine was extracted by shaking the alkaline diluted plasma with 2.5 ml toluene

in the test tubes, which were tightly stoppered with glass stoppers, for 30 min. in a "Luckham" rotary mixer at approximately 150 cycles per minute. After centrifugation at 2000 g for 5 min. 2.0 ml of the toluene extract was transferred to a fresh test tube. A 10 µl portion of a freshly prepared 1% (v/v) solution of trichloroacetyl chloride in toluene was added and the tube tightly stoppered. The amphetamine in the extract was allowed to react with the trichloroacetyl chloride in a water bath at 40°C for 60 min. to form 1-phenyl-2-(trichloroacetamido)-propane. It was found that the incubation time of 30 min. recommended by Anggard et al. (1970) was inadequate for completion of the reaction since increasing the interval before the chromatography of the reacted sample led to an increase in the chromatography reading. This did not occur when the reaction was allowed to proceed for 60 min.

Incubated samples were allowed to cool to room temperature before being injected into the gas chromatograph. A Hewlett-Packard gas liquid chromatograph model S710A with ^{63}Ni; (15mCi) electron capture detector was used. A 2 metre long 4 mm internal diameter glass column was used, packed with 5% OV 17 on 100/120 mesh diatomite W AW DMCS. The operating conditions for the chromatography were as follows: Injection port temperature 200°C, oven temperature 200°C, detector temperature 200°C. The carrier gas used was argon/methane (90/10 v/v) at a flow rate of 40 ml/min. An internal standardization technique was not used. (Anggard et al. found that technique to have the disadvantage of variation of detector response factors to standard and to

amphetamine at different levels of sensitivity). Therefore a great degree of care was taken to ensure accurate injection into the column. The "solvent flush technique" was used (Anggard et al. 1970). This involved taking up 1.0 µl toluene, 0.5 µl air, 4 µl of the sample and finally 1 µl of air into a 10 µl Hamilton syringe. The entire contents of the syringe were then injected into the column, the sample being flushed in by air and solvent.

A calibration curve was obtained from measurements of known amounts of amphetamine sulphate added to plasma from untreated animals. A separate calibration curve was also produced on one occasion using amphetamine standards made up in water instead of plasma. Amphetamine concentrations in the samples were read off directly from the calibration curve produced on the occasion of the assay of each batch of samples. In determining the gas chromatographic response the peak height was measured in mm. This occurred at 11½ min. following injection into the column.

(b) Estimation of Amphetamine in Brain

Whole brain was homogenized in 0.4M perchloric acid (3 ml/gram tissue) and proteins and cell debris removed by centrifugation for 15 min. at 10,000 g in an MSE Mistral II centrifuge. A 2.0 ml portion of the extract was transferred to a siliconized test tube, mixed with 200 µl 5M NaOH and 2.5 ml toluene added. Thereafter the procedure followed that for plasma. Calibration curves were obtained from analysis of brain tissue extracts from untreated animals to which known amounts of amphetamine had been added. Amphetamine concentrations in the samples were read off directly from such a calibration curve.

7. SOURCES OF DRUGS AND CHEMICALS

The drugs administered to animals in this study are listed below, with sources and certain trade names in brackets:

Apomorphine hydrochloride ampoules containing 3 mg/ml in sterile water 'for injection' containing 0.1% sodium metabisulphite (Evans Medical); DL-amphetamine sulphate (L. Light and Co.: Smith, Kline and French); benztropine mesylate (Merck, Sharp and Dohme); chlorimipramine hydrochloride (Geigy Pharmaceuticals); desmethylimipramine hydrochloride (Geigy Pharmaceuticals); dopamine hydrochloride (Sigma); GEA 654 ("Alaprocate", Astra Pharmaceuticals); haloperidol ampoules containing 5 mg/ml in water 'for injection' containing lactic acid 5.83 mg/ml and 8 mg/ml sodium chloride ("Serenace", Searle); 6-hydroxy-dopamine hydrobromide (Goteborg); 5-hydroxytryptamine bimaleinate (British Drug Houses); LRCL 5182 (Eli Lilly and Co.); 5-methoxy-N,N,-dimethyltryptamine (Sigma); methysergide hydrogen maleinate (Sandoz); nialamide ('Niamid', Pfizer); L-noradrenaline hydrochloride (Sigma); phenoxybenzamine hydrochloride (Smith, Kline and French); 'SKF -525A' (Smith, Kline and French).

S-adenosyl-L- (^{3}H-methyl) methionine 9.2 - 12.6 Cl/m.mol was obtained from The Radiochemical Centre, Amersham. "Liquifluor" scintillant was obtained from New England Nuclear Ltd. and "NE 260" scintillant from Nuclear Enterprises Ltd. A catechol - O -methyl transferase preparation prepared in the department according to the method of Axelrod and Tomchick (1958) was kindly supplied

by Mrs. A. K. Wright. Toluene "special for chromatography" was obtained from British Drug Houses. All other reagents used in biochemical estimations were of analytical grade.

III RESULTS

A. DRUG STUDIES

1. Dose-response curve to DL-Amphetamine Sulphate

Animals were studied on the hole-board for two hours immediately following injection of 2,4 or 8 mg/kg of DL-amphetamine sulphate or of 1 ml/kg saline i.p.

The results are presented in Figs. 16 and 17, Tables 1 & 2. Behaviour following an injection of saline 1 ml/kg was similar to that observed previously. An initial burst of "exploratory" dipping and locomotion was observed during the first 10 minutes. Thereafter there was a low, fluctuating level of both types of dipping and of locomotion (Fig.16a). DL-amphetamine 2 mg/kg produced a small stimulation of dipping, predominantly of the "exploratory" type as well as a slight increase in locomotion (Fig.16b, Table 1). DL-amphetamine at a dose of 4 mg/kg produced a much greater stimulation of "exploratory" dipping and locomotion (Fig.16c). "Stereotyped" dipping was less markedly stimulated and the S/T ratio was correspondingly low. At a dose of 8 mg/kg, an initial stimulation of "exploratory" dipping and locomotion was followed by a progressive and marked stimulation of "stereotyped" dipping with inhibition of "exploratory" dipping and locomotion (Fig.16d). With increasing dosage of DL-amphetamine the initial burst of "exploratory" dipping was enhanced. With increasing dosage of amphetamine the overall level of dipping continued to increase markedly (Fig. 17). The 'S/T'

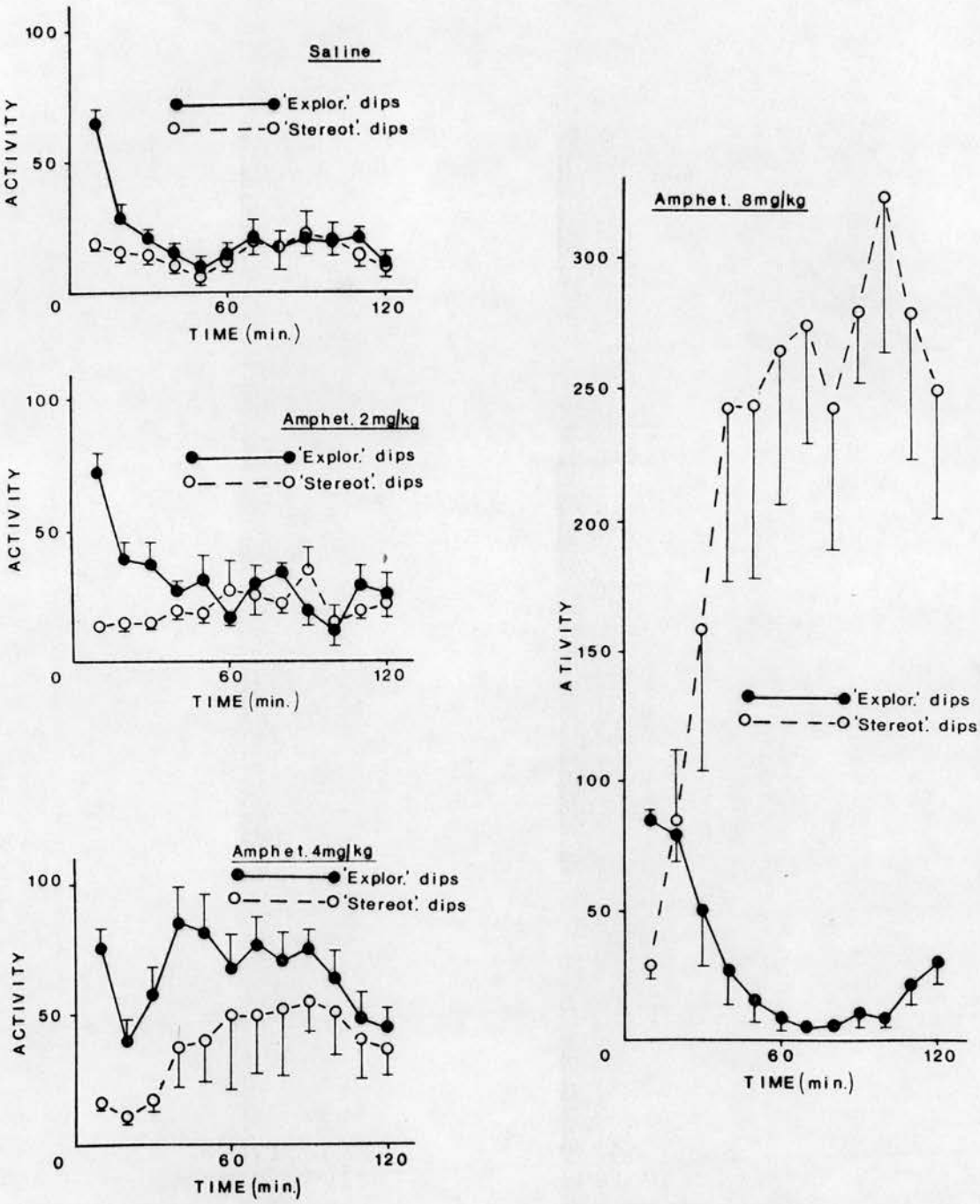


FIG. 16: Behaviour in the hole-board apparatus following i.p. administration of 1 ml/kg saline or 2, 4 or 8 mg/kg DL-amphetamine sulphate. Each point represents mean activity (no. of hole dips) of six rats ± standard error of the mean (S.E.M.) during successive 10 min. intervals following the injection.

TABLE 1: Behaviour of rats in the hole-board apparatus following administration of 1 ml/kg saline or 2, 4 or 8 mg/kg DL-amphetamine sulphate i.p. Figures denote mean activity ± standard error of the mean (S.E.M.) during successive 10 min. intervals after injection. Six animals were studied at each dose level.

S - number of "stereotyped" dips; E - number of "exploratory" dips; LOC - number of locomotor counts. (see page 61).

TIME INTERVAL (min)	0 - 10			10 - 20		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	18 ± 2	64 ± 5	48 ± 5	16 ± 4	28 ± 6	31 ± 6
2	13 ± 2	72 ± 7	59 ± 3	15 ± 4	38 ± 7	37 ± 9
4	16 ± 3	75 ± 8	64 ± 8	11 ± 3	39 ± 8	36 ± 6
8	29 ± 5 *	84 ± 9	41 ± 7 *	84 ± 27 ***	78 ± 11	25 ± 8
TIME INTERVAL (min)	20 - 30			30 - 40		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	14 ± 4	21 ± 4	30 ± 6	10 ± 3	15 ± 4	18 ± 6
2	14 ± 3	37 ± 9	50 ± 17	19 ± 5	27 ± 5	37 ± 15
4	17 ± 4	57 ± 10	62 ± 9	37 ± 16	84 ± 14	52 ± 8
8	158 ± 55	50 ± 21	18 ± 10 *	242 ± 65 ***	27 ± 13 **	14 ± 6 **
TIME INTERVAL (min)	40 - 50			50 - 60		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	6 ± 3	10 ± 4	9 ± 4	12 ± 4	13 ± 4	14 ± 5
2	18 ± 5	31 ± 9	23 ± 8	27 ± 12	16 ± 4	24 ± 6
4	39 ± 15	81 ± 16	44 ± 11	48 ± 28	67 ± 13	53 ± 6
8	243 ± 66 **	14 ± 8 ***	7 ± 3 **	265 ± 58	8 ± 5 ***	2 ± 1 ***

* $p < 0.05$
** $p < 0.02$
*** $p < 0.01$

(Kruskal -Wallis one-way analysis of variance)

(Details of the responses of individual rats can be found in the Appendix - Tables 1-4).

(Contd.)

TABLE 1: continued

TIME INTERVAL (min)	60 - 70			70 - 80		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	19 ± 5	21 ± 7	19 ± 5	17 ± 9	17 ± 5	12 ± 4
2	24 ± 8	29 ± 8	19 ± 6	22 ± 5	34 ± 5	18 ± 4
4	49 ± 22	76 ± 11	51 ± 4	51 ± 25	70 ± 11	57 ± 6
8	274 ± 46 ***	5 ± 2 ***	1 ± 1 ****	242 ± 54 ***	6 ± 2 ****	6 ± 3 ****
TIME INTERVAL (min)	80 - 90			90 - 100		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	22 ± 7	20 ± 6	16 ± 4	20 ± 5	18 ± 5	17 ± 4
2	35 ± 9	19 ± 5	19 ± 4	15 ± 7	12 ± 6	12 ± 7
4	53 ± 16	74 ± 8	55 ± 7	50 ± 16	63 ± 11	51 ± 16
8	279 ± 27 ***	10 ± 5 ***	16 ± 13 ***	323 ± 59 ***	8 ± 3 ***	7 ± 4 ***
TIME INTERVAL (min)	100 - 110			110 - 120		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	14 ± 4	21 ± 5	18 ± 5	10 ± 4	12 ± 4	17 ± 6
2	19 ± 4	28 ± 8	19 ± 6	22 ± 6	26 ± 8	17 ± 7
4	39 ± 15	47 ± 10	48 ± 16	36 ± 10	44 ± 9	51 ± 20
8	278 ± 55 ***	21 ± 7	10 ± 4	249 ± 48 ***	30 ± 9	22 ± 14

*** $p < 0.01$

**** $p < 0.001$

(Kruskal-Wallis one-way analysis of variance)

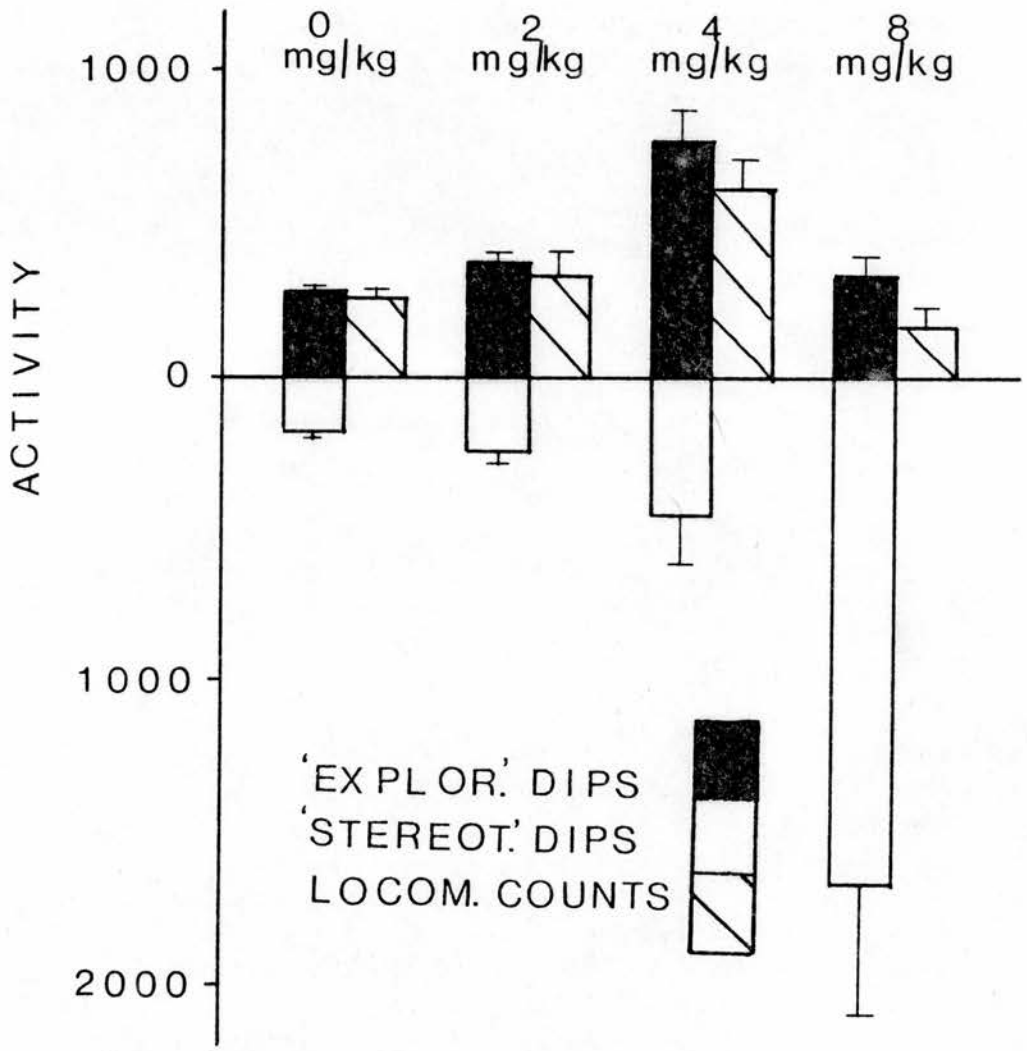


FIG. 17: Overall behaviour in the hole-board apparatus during a two-hour period following i.p. administration of 1 ml/kg saline or 2, 4 or 8 mg/kg DL-amphetamine sulphate. Each column represents mean activity (No. of dips or locomotor counts) of six rats.

± Standard error of the mean (S.E.M.) during the entire period.

TABLE 2: Overall behavioural response in the hole-board apparatus during a 2-hour period following administration of 1 ml/kg saline, or 2, 4 or 8 mg/kg DL-amphetamine sulphate. Figures show the response of each of a group of six animals under any one treatment. A total of 24 animals were thus employed in the experiment.

S - "Stereotyped" dips; E - "Exploratory" dips: T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts (see page 61).

DOSE (mg/kg)	ACTIVITY	RAT NO.						MEAN ± SEM
		1	2	3	4	5	6	
0 (Saline 1 ml/kg)	S	132	107	239	246	211	141	179 ± 24
	E	265	191	274	350	307	178	261 ± 26
	T	397	298	513	596	518	319	440 ± 49
	S/T	0.33	0.36	0.47	0.41	0.41	0.44	0.40 ± 0.02
	LOC	287	150	211	386	187	284	251 ± 35
2	S	149	181	272	474	177	207	243 ± 49
	E	534	175	340	491	326	351	369 ± 53
	T	683	356	612	965	503	558	613 ± 84
	S/T	0.22	0.51	0.44	0.49	0.35	0.37	0.40 ± 0.04
	LOC	629	209	294	-	209	300	328 ± 77
4	S	163	242	1306	366	228	374	446 ± 175
	E	862	771	518	566	862	1098	779 ± 88
	T	1025	1013	1824	932	1090	1472	1226 ± 142
	S/T	0.16	0.24	0.72	0.39	0.21	0.25	0.33 ± 0.08
	LOC	894	509	759	497	-	467	625 ± 83
8	S	3666	2296	941	2790	4106	2209	2668 ± 462
	E	475	349	339	162	171	555	342 ± 64
	T	4141	2645	1280	2952	4277	2764	3010 ± 450
	S/T	0.89	0.87	0.74	0.95	0.96	0.80	0.87 ± 0.04
	LOC	334	-	69	81	26	344	171 ± 69

A Kruskal-Wallis one-way analysis of variance showed that the behavioural responses produced by the four treatments were significantly different ($p < 0.01$ for "stereotyped" dips for "exploratory" dips, the S/T ratio and locomotor counts).

ratio fell at a dosage of 4 mg/kg and then increased markedly at 8 mg/kg. (Table 2).

A Kruskal-Wallis one-way analysis of variance showed that the differences in results between the four treatment groups for the entire 2-hour observation period were statistically significant ($p < 0.01$ for "exploratory" dips, $p < 0.01$ for "stereotyped" dips, $p < 0.01$ for locomotor counts and $p < 0.01$ for the S/T ratio).

For different 10-minute intervals the results for all three behavioural parameters were significant in the majority of time-intervals (Table 1).

(2) <u>Responses at repeated weekly treatments with (a) DL-amphetamine sulphate 4 mg/kg i.p. on six occasions or (b) saline 1 ml/kg i.p. on three occasions followed by DL-amphetamine sulphate 4 mg/kg.</u>

Six animals were studied for one hour on the hole-board following injection of 4 mg/kg DL-amphetamine sulphate on six occasions at exactly weekly intervals. A further six animals were given three injections of 1 ml/kg physiological saline followed by three injections of 4 mg/kg DL-amphetamine, the injections all taking place at weekly intervals.

The results are presented in Figs. 18 and 19 and Tables 3 and 4. Repeated weekly treatment with amphetamine led to a continuing increase in "stereotyped" dipping response accompanied by a decrease in "exploratory" dipping after a slight initial increase which was not statistically significant. Locomotor counts also

TABLE 3: Changes in the behavioural response to 4 mg/kg DL-amphetamine sulphate during the course of repeated weekly i.p. administrations of the drug. Each column represents the response of one rat during successive weekly recording for one hour following drug administration. A total of 6 animals were thus employed in the experiment.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

WEEK NO	TREATMENT	ACTIVITY	RAT NO. 1	3	5	8	10	12	MEAN ± SEM
1	Amphet. 4 mg/kg	S	312	72	227	280	139	128	193 ± 38
		E	977	128	650	626	512	582	579 ± 112
		T	1289	200	877	906	651	710	772 ± 147
		S/T	0.24	0.36	0.26	0.31	0.21	0.18	0.26 ± 0.02
		LOC	397	116	469	361	162	277	297 ± 56
2	"	S	434	268	799	579	581	104	461 ± 101
		E	906	541	343	373	926	774	635 ± 105
		T	1340	809	1142	952	1507	878	1105 ± 113
		S/T	0.32	0.33	0.70	0.61	0.39	0.12	0.41 ± 0.09
		LOC	535	218	632	280	509	325	416 ± 67
3	"	S	469	412	631	970	994	729	701 ± 100
		E	955	601	238	61	551	871	546 ± 142
		T	1424	1013	869	1031	1545	1600	1247 ± 128
		S/T	0.33	0.41	0.73	0.94	0.64	0.46	0.58 ± 0.09
		LOC	42	156	814	48	154	109	220 ± 120
4	"	S	816	218	876	318	*-	790	604 ± 136
		E	117	543	59	84	-	881	337 ± 162
		T	933	761	935	402	-	1671	940 ± 207
		S/T	0.87	0.29	0.94	0.79	-	0.47	0.67 ± 0.13
		LOC	11	81	164	92	-	151	100 ± 28
5	"	S	356	260	1422	184	521	1319	677 ± 225
		E	494	387	164	47	185	505	297 ± 78
		T	850	647	1586	231	706	1824	974 ± 248
		S/T	0.42	0.40	0.90	0.80	0.74	0.72	0.66 ± 0.09
		LOC	32	172	132	39	29	68	79 ± 24
6	"	S	1231	120	1540	1703	484	798	979 ± 253
		E	15	202	14	23	258	469	163 ± 74
		T	1246	322	1554	1726	742	1267	1143 ± 214
		S/T	0.99	0.37	0.99	0.99	0.65	0.63	0.77 ± 0.11
		LOC	11	14	53	60	74	147	60 ± 21

* Record spoilt

Kruskal-Wallis one-way analysis of variance: $p < 0.05$ for "stereotyped" dips; < 0.05 for "exploratory" dips; < 0.001 for S/T ratio; < 0.01 for locomotor counts.

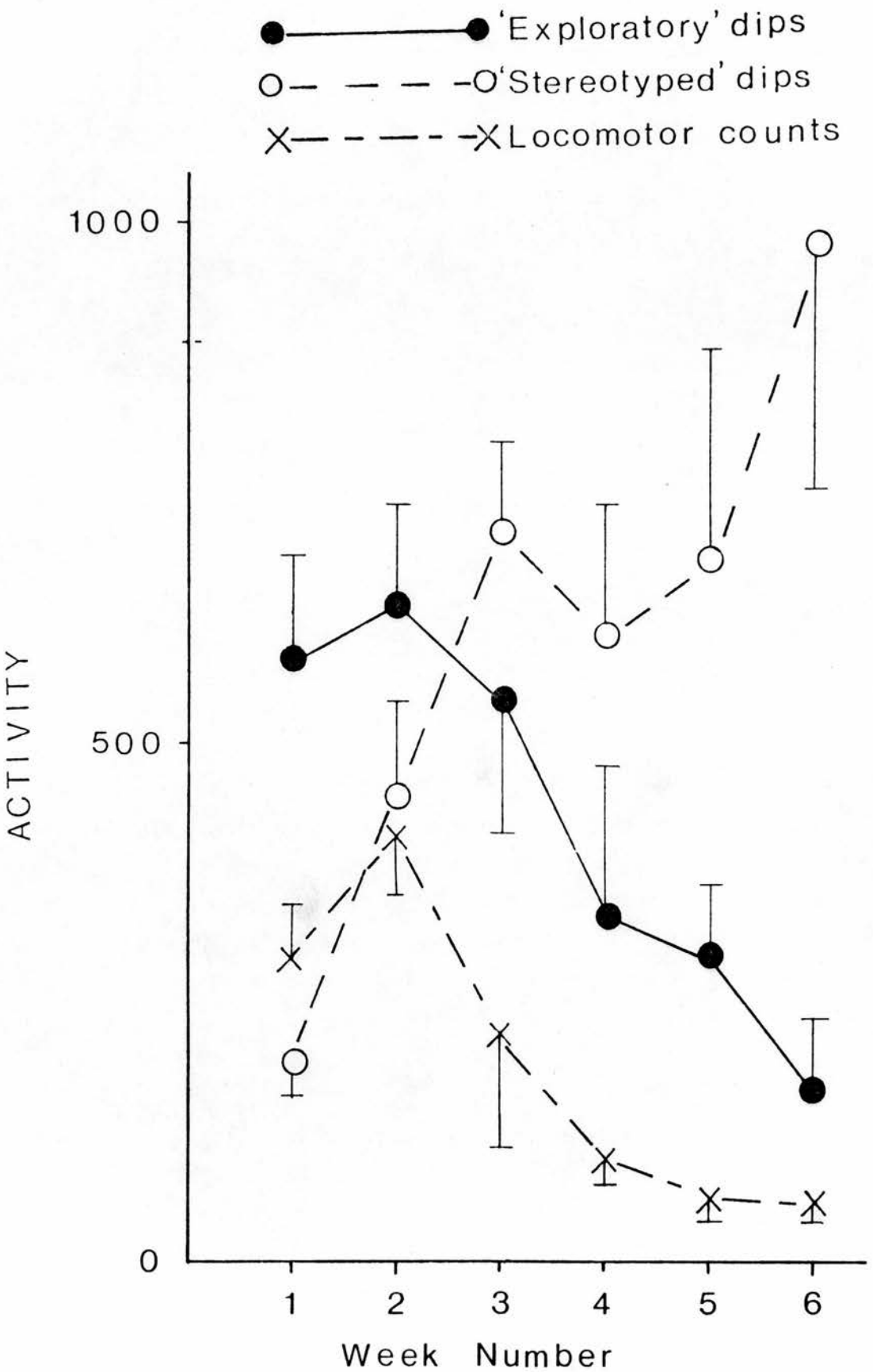


FIG. 18: Behavioural response on the hole-board of six rats following i.p. administration of 4 mg/kg DL-amphetamine sulphate at weekly intervals. Each point represents mean activity (No. of dips or locomotor counts) ± S.E.M. over a one-hour period following the injection.

TABLE 4: Behavioural responses of six rats to successive weekly administration of 1 ml/kg physiological saline on three occasions followed by 4 mg/kg DL-amphetamine sulphate on three occasions. Each column represents the behavioural responses by one animal to the six treatments during a period of one hour following drug administration.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

WEEK No	TREAT-MENT	ACTIVITY	RAT NO.						MEAN ± SEM
			2	4	6	7	9	11	
1	Saline 1 ml/kg	S	18	30	34	6	100	83	45 ± 15
		E	119	107	141	43	176	189	129 ± 22
		T	137	137	175	49	276	272	174 ± 36
		S/T	0.13	0.22	0.19	0.12	0.36	0.31	0.22 ± 0.04
		LOC	197	80	249	87	131	147	148 ± 26
2	"	S	74	85	50	19	126	98	75 ± 15
		E	143	168	123	55	125	88	117 ± 16
		T	217	253	173	74	251	186	192 ± 27
		S/T	0.34	0.34	0.29	0.26	0.50	0.53	0.38 ± 0.05
		LOC	130	92	185	121	108	132	128 ± 13
3	"	S	97	73	134	43	90	62	83 ± 13
		E	193	178	71	87	104	124	126 ± 19
		T	290	251	205	130	194	186	209 ± 23
		S/T	0.33	0.29	0.65	0.33	0.46	0.33	0.40 ± 0.06
		LOC	206	80	63	149	48	96	107 ± 24
4	Amphet. 4 mg/kg	S	68	18	207	164	733	487	279 ± 113
		E	182	183	902	815	226	505	469 ± 134
		T	250	201	1109	979	959	992	748 ± 166
		S/T	0.27	0.09	0.19	0.17	0.76	0.49	0.33 ± 0.10
		LOC	211	61	83	467	66	217	184 ± 64
5	"	S	42	21	386	201	1166	419	372 ± 173
		E	151	183	1066	741	39	139	386 ± 170
		T	193	204	1452	942	1205	558	759 ± 215
		S/T	0.22	0.10	0.27	0.21	0.97	0.75	0.42 ± 0.14
		LOC	265	83	-	499	10	34	178 ± 90
6	"	S	93	232	479	97	948	306	359 ± 131
		E	89	186	877	164	44	103	244 ± 128
		T	182	418	1356	261	992	409	603 ± 191
		S/T	0.51	0.56	0.35	0.37	0.96	0.75	0.58 ± 0.10
		LOC	211	64	415	244	22	42	166 ± 62

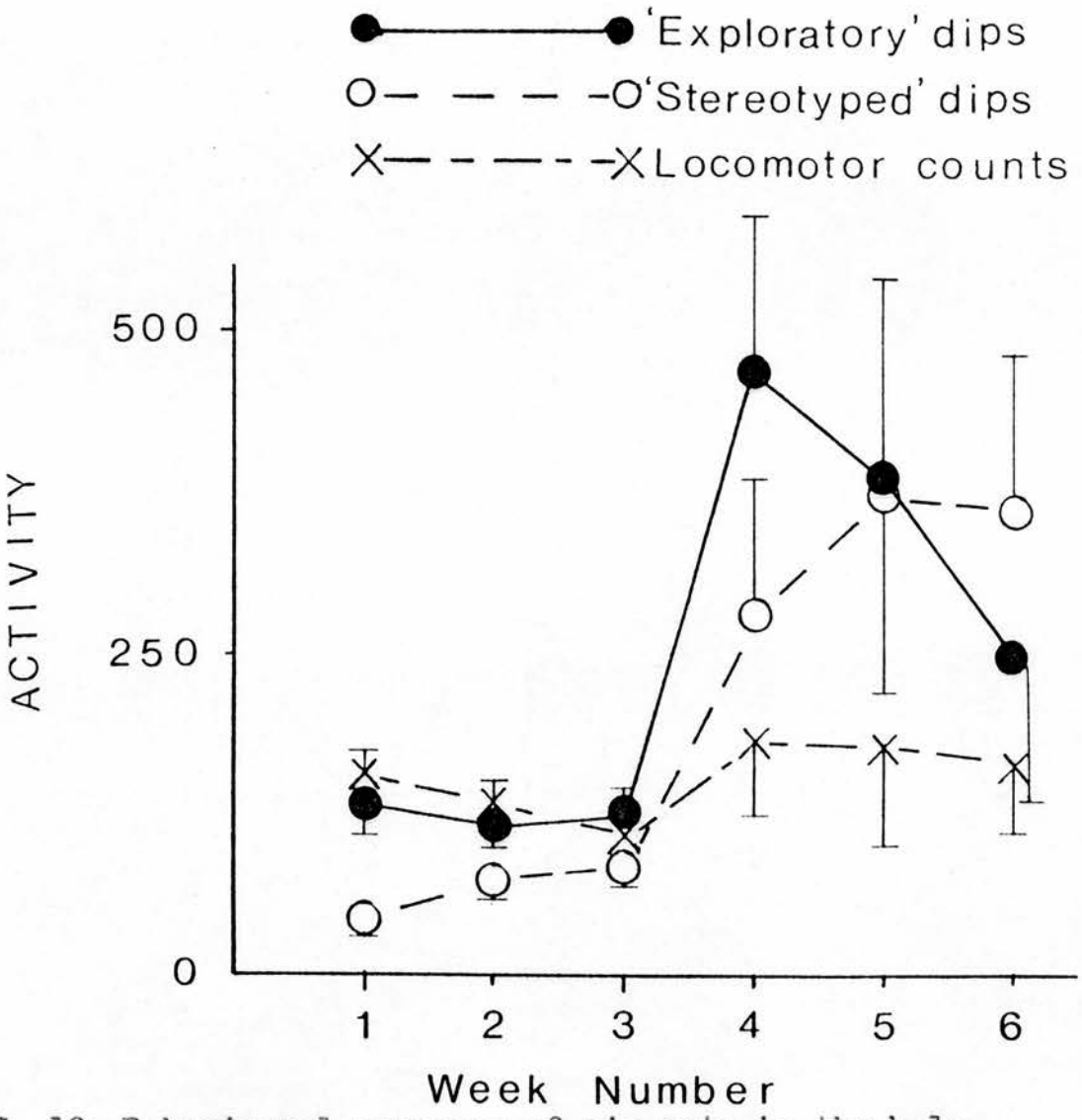


FIG. 19: Behavioural response of six rats in the hole-board apparatus following weekly i.p. administration of 1 ml/kg saline at weekly intervals for three weeks (week nos. 1-3) and followed by weekly i.p. administration of 4 mg/kg for three weeks (week nos. 4-6). Each point represents mean activity (No. of dips or locomotor counts) ± S.E.M. over a one-hour period following injection.

progressively decreased after a small initial increase which was not significant and the S/T ratio progressively increased. These results are consistent with an increasing sensitivity to the effects of the amphetamine since the changes are similar to those produced by an increase in amphetamine dosage in groups of naive animals (see previous section). A Kruskal-Wallis one-way analysis of variance showed that the behavioural changes were statistically significant ($p < 0.05$ for "stereotyped" dips, < 0.05 for "exploratory" dips, < 0.01 for the 'S/T' ratio and < 0.01 for locomotor counts).

Responses to the first dose of amphetamine were markedly different in the six animals (Table 3). When the results were 'normalized' by expressing the results of each animal during the subsequent five trials as a percentage of the initial response, the same differences in behavioural response over the six treatments was obtained. However, the changes in "exploratory" dipping were no longer statistically significant whereas the changes in "stereotyped" dipping and locomotor counts were both significant ($p < 0.01$).

Over three successive injections, there was no alteration in the response to weekly saline administration (Fig. 19, Table 4). The expected increase in hole-dipping and locomotor counts to amphetamine given at the fourth injection was seen. This response appeared less intense thanthat seen on the fourth treatment in the group of rats that were given amphetamine throughout (see Fig.18), but these differences were not statistically significant.

The response appeared only slightly different from that seen on day 1 in the group treated with amphetamine throughout and this difference was not statistically significant. During the period of the three successive amphetamine treatments in the saline pretreated rats there were minor trends towards an increase in "stereotyped" dipping response, decrease in "exploratory" dipping and locomotor counts and increase in 'S/T' ratio, these trends however were not statistically significant in any of the four parameters.

(3) Effect of haloperidol pretreatment on the behavioural response to an injection of saline and to the injection of 8 mg/kg DL-amphetamine sulphate

Animals were pretreated with an intraperitoneal injection of 0.05, 0.1, 0.2 or 0.4 mg/kg haloperidol 20 minutes before an injection of 1 ml/kg physiological saline or 8 mg/kg DL-amphetamine sulphate i.p. The results were compared with those from animals in experiment 1 above, which were treated with saline or 8 mg/kg DL-amphetamine sulphate with no pretreatment.

On "spontaneous" behaviour (rats injected with 1 ml/kg saline) haloperidol produced a dose-dependent reduction in both forms of dipping as well as in locomotor counts (Fig. 20, Table 5). At doses of 0.2 and 0.4 mg/kg haloperidol, all behaviour was almost totally eliminated. These results were shown to be highly significant using the Kruskal-Wallis one-way analysis of variance ($p < 0.001$ for "stereotyped" dips and "exploratory" dips, < 0.05 for 'S/T' ratio and < 0.01 for locomotor counts).

TABLE 5: Effects of pretreatment with haloperidol on the behavioural response to administration of saline. Animals were pretreated with 0.05, 0.1, 0.2 or 0.4 mg/kg i.p. haloperidol 20 min. before administration of 1 ml/kg saline i.p., following which their behaviour was recorded in the hole-board apparatus for two hours. The figures represent the overall activity during the two hour period in these animals as well as the response of non-pretreated control animals to acute saline administration.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

HALOPERIDOL DOSE (mg/kg)	ACT-IVITY	RAT NO. 1	2	3	4	5	6	7	MEAN ± SEM
0 (No pretreatment)	S	132	107	239	246	211	141		179 ± 24
	E	265	191	274	350	307	178		261 ± 26
	T	397	298	513	596	518	319		440 ± 49
	S/T	0.33	0.36	0.47	0.41	0.41	0.44		0.40 ± 0.02
	LOC	287	150	211	386	187	284		251 ± 35
0.05	S	169	111	168	162	107	165		147 ± 12
	E	161	219	227	268	181	253		218 ± 16
	T	330	330	395	430	288	418		365 ± 23
	S/T	0.51	0.34	0.43	0.38	0.37	0.39		0.40 ± 0.02
	LOC	221	156	236	206	209	293		220 ± 18
0.1	S	127	137	151	172	19			121 ± 26
	E	154	259	261	264	59			199 ± 39
	T	281	396	412	436	78			321 ± 65
	S/T	0.45	0.35	0.37	0.39	0.24			0.36 ± 0.03
	LOC	271	227	310	217	291			263 ± 18
0.2	S	15	25	26	25	32	21	47	27 ± 4
	E	59	67	79	62	54	27	150	71 ± 14
	T	74	92	105	87	86	48	197	98 ± 17
	S/T	0.20	0.27	0.25	0.29	0.37	0.44	0.24	0.29 ± 0.03
	LOC	39	68	74	-	-	64	215	92 ± 31
0.4	S	14	5	31	2	11	3	5	10 ± 4
	E	40	11	34	13	46	16	22	26 ± 5
	T	54	16	65	15	57	19	27	36 ± 9
	S/T	0.26	0.31	0.48	0.13	0.19	0.16	0.19	0.25 ± 0.04
	LOC	79	3	-	112	-	42	-	52 ± 21

Kruskal-Wallis one-way analysis of variance: $p < 0.001$ for "stereotyped" dips and "exploratory" dips < 0.05 for S/T ratio, < 0.01 for locomotor counts.

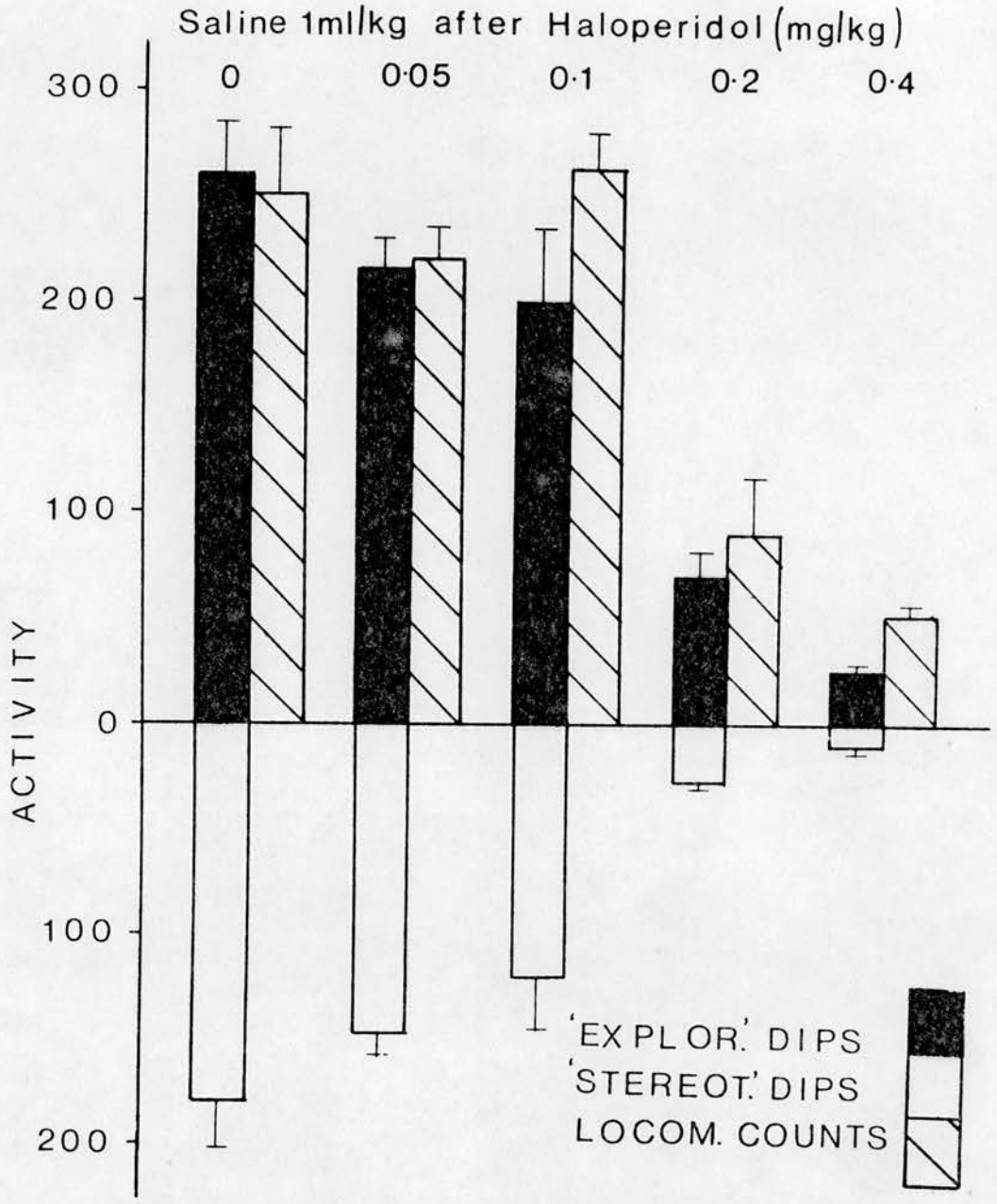


FIG. 20: Effects of pretreatment with 0.05, 0.1, 0.2 or 0.4 mg/kg haloperidol i.p. on the behavioural response in the hole-board apparatus following i.p. administration of 1 ml/kg saline. The results are compared with the response to saline without any pretreatment (dose "0"). Each column represents the mean activity ± S.E.M. of 5-7 rats during a 2-hour period immediately following the saline injection.

Haloperidol reduced the response to 8 mg/kg DL-amphetamine in a dose-related manner (Fig.21, Table 6 which present the results obtained following pretreatment with different doses of haloperidol as well as those obtained following no pretreatment with this drug.) At the two highest doses of haloperidol (0.2 and 0.4 mg/kg) the response to amphetamine is essentially completely blocked. A dose of 0.1 mg/kg proved more effective in blocking "stereotyped" dips than "exploratory" dips and locomotion. A striking feature of Fig. 21 is that the graph representing the dose-related effects of haloperidol on the amphetamine response is more or less a mirror image of the dose-response curve to DL-amphetamine shown beside it. A Kruskal-Wallis one-way analysis of variance showed that the quantitative differences in response to amphetamine with the different doses of haloperidol and with no pre-treatment were significant ($p < 0.001$ for "stereotyped" and "exploratory" dips, the S/T ratio and locomotor counts.

(4) <u>Modification by chronic haloperidol pretreatment of the behavioural response following administration of saline or 4 mg/kg DL-amphetamine sulphate</u>

Two different experiments were performed, the first employing a dosage of 1 mg/kg haloperidol daily, the second employing dosages of 5 mg/kg daily.

(a) Animals were divided initially into two groups of 12 rats each. The first group received an injection of 1 ml/kg saline daily for 10 days (days 1-10) followed by a 'rest' day when no treatment was administered (day 11).

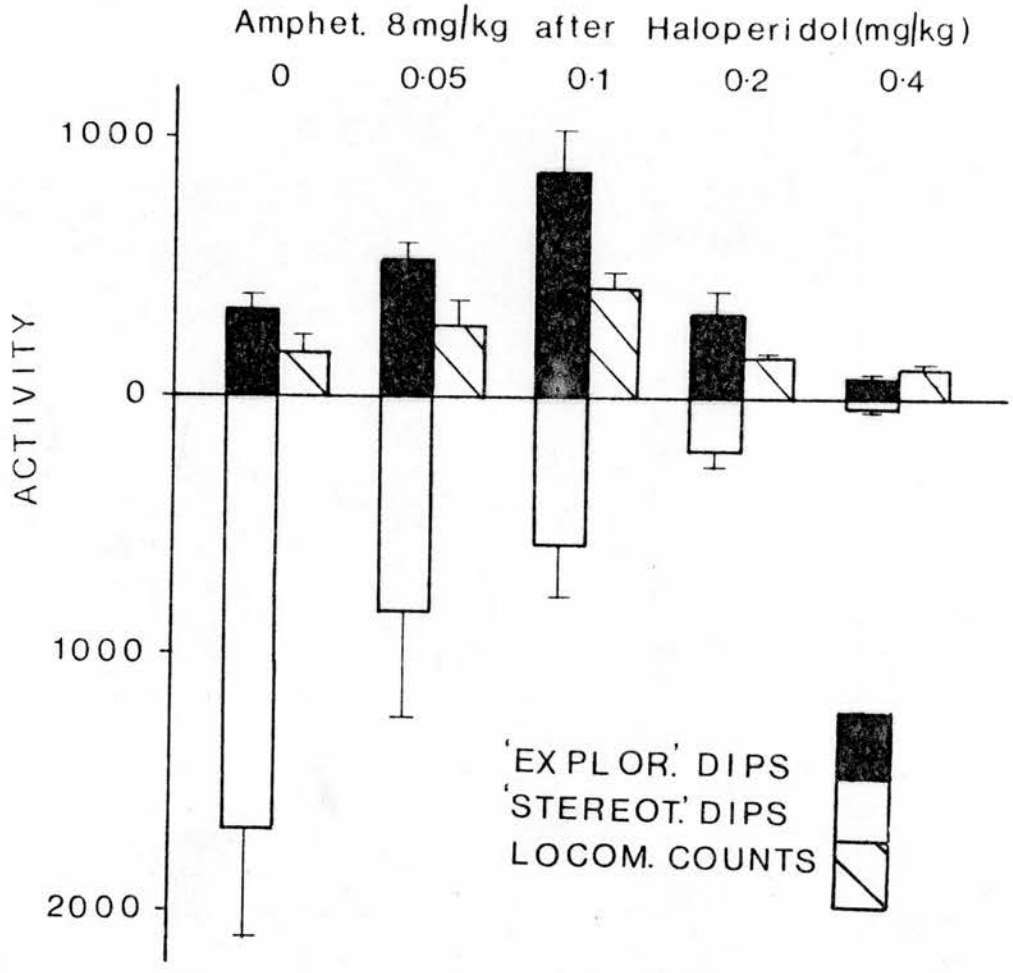


FIG. 21a: Effect of pretreatment with 0.05, 0.1, 0.2 or 0.4 mg/kg haloperidol i.p. on the behavioural response in the hole-board apparatus following i.p. administration of 8 mg/kg DL-amphetamine sulphate. The results are compared with the response to amphetamine without any pretreatment (dose "0"). Each column represents the mean activity ± S.E.M. of 4-7 rats during a 2-hour period immediately following the amphetamine injection. (Compare with Fig. 21b on opposite page).

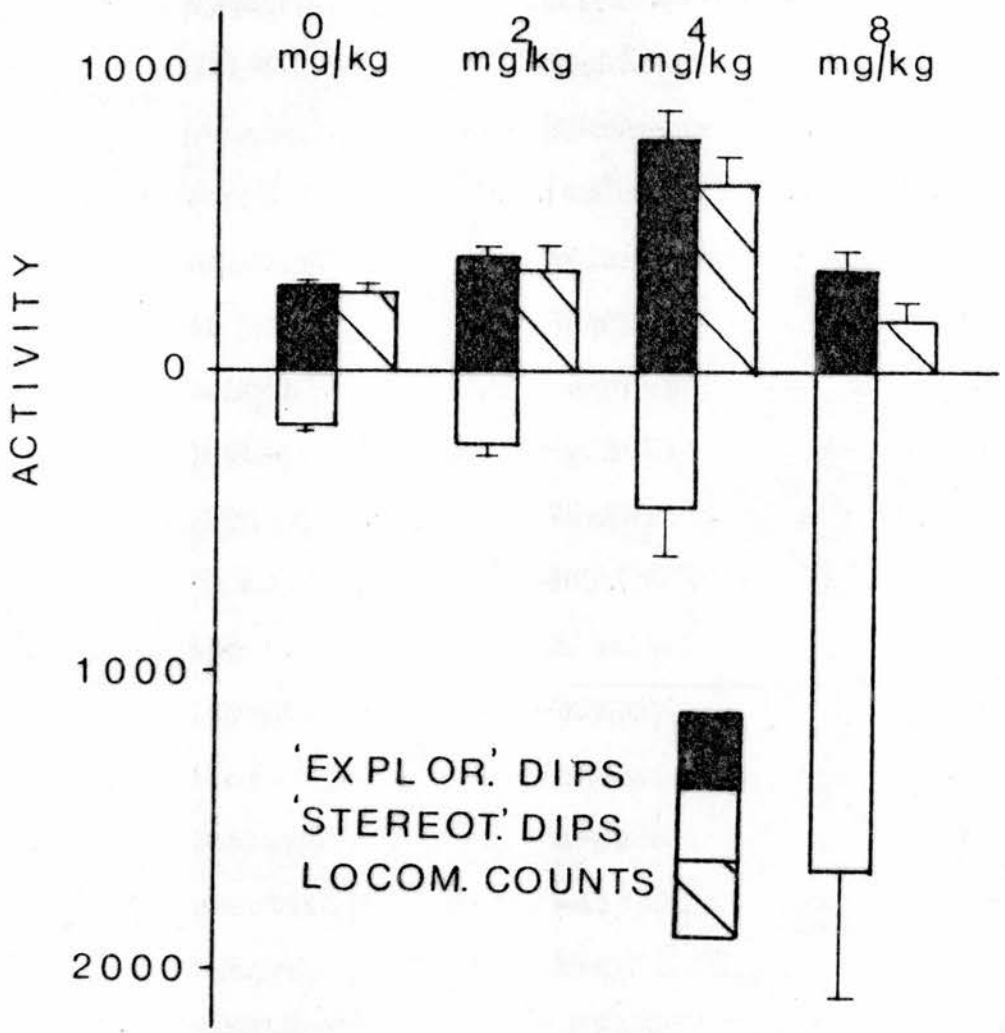


FIG. 21b: Overall behaviour during a two hour period following i.p. administration of 1 ml/kg saline ("0 mg/kg") or 2, 4 or 8 mg/kg DL-amphetamine sulphate. Six animals were studied at each dose. There is a striking similarity between this figure and that of the modification by haloperidol of the response to 8 mg/kg amphetamine on the opposite page (Fig. 21a).

TABLE 6: Effects of pretreatment with haloperidol on the behavioural response to administration of 8 mg/kg DL-amphetamine sulphate. Animals were pretreated with 0.05, 0.1, 0.2 or 0.4 mg/kg i.p. haloperidol 20 min. before administration of 8 mg/kg DL-amphetamine sulphate i.p., following which their behaviour was recorded in the hole-board apparatus for two hours. The figures represent the overall activity during the two hour period in these animals as well as the response of non-pretreated control animals to acute saline administration.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

HALOPERIDOL DOSE (mg/kg)	ACT-IVITY	RAT NO.								MEAN ± SEM
		1	2	3	4	5	6			
0 (No pre-treatment	S	3666	2296	941	2790	4106	2209			2668 ± 462
	E	475	349	339	162	171	555			342 ± 64
	T	4141	2645	1280	2952	4277	2764			3010 ± 450
	S/T	0.89	0.87	0.74	0.95	0.96	0.80			0.87 ± 0.04
	LOC	334	-	69	81	26	344			171 ± 69
0.05	S	1023	654	2297	2556					1632 ± 468
	E	459	770	394	553					544 ± 82
	T	1482	1424	2691	3109					2176 ± 426
	S/T	0.69	0.46	0.85	0.82					0.70 ± 0.09
	LOC	344	590	116	66					279 ± 120
0.1	S	251	390	1850	90	366	590	476		573 ± 221
	E	678	1525	199	628	689	1286	1125		876 ± 112
	T	929	1915	2049	718	1055	1876	1601		1449 ± 204
	S/T	0.27	0.20	0.90	0.13	0.35	0.31	0.30		0.35 ± 0.10
	LOC	615	532	259	239	293	647	394		426 ± 65
0.2	S	190	152	552	117	118	73			200 ± 72
	E	408	259	702	280	214	113			329 ± 84
	T	598	411	1254	397	332	186			530 ± 154
	S/T	0.32	0.37	0.44	0.29	0.36	0.39			0.36 ± 0.02
	LOC	261	104	208	176	95	121			161 ± 27
0.4	S	15	16	55	73	46	51	10	27	37 ± 9
	E	49	64	92	139	84	142	29	81	85 ± 14
	T	64	80	147	212	130	193	39	108	122 ± 1
	S/T	0.23	0.20	0.37	0.34	0.35	0.26	0.26	0.25	0.28 ± 0.02
	LOC	119	152	-	85	154	156	58	136	123 ± 14

Kruskal-Wallis one-way analysis of variance: $p < 0.001$ for "stereotyped" dips, "exploratory" dips, S/T ratio and locomotor counts.

The following day (day 12) six animals were studied on the hole-board for one hour following an injection of 1 ml/kg saline while the other six were studied following administration of 4 mg/kg DL-amphetamine sulphate. A second group of 12 rats was treated with daily injections of 1 mg/kg haloperidol for 10 days (days 1-10). Thereafter this group was treated in identical fashion to the group treated with daily saline injections.

There was no difference between the "chronic saline" and "chronic haloperidol" groups in the behavioural response following saline injection (Fig.22, Table 7). Following an injection of 4 mg/kg DL-amphetamine sulphate the "chronic haloperidol" group showed a greater increase in dipping activity compared with the "chronic saline" group (Fig.22 Table 7). This increase involved "stereotyped" more than "exploratory" dipping so that the S/T ratio was increased. Locomotor counts were also greater in the chronic haloperidol group. None of these differences was statistically significant.

(b) In a subsequent experiment, animals were divided into two groups of ten each. Each animal in the first group received an i.p. injection of 1 ml/kg saline daily for 6 days (days 1-6), while the second group received 5 mg/kg haloperidol daily for six days. There was then a treatment-free interval of three days following which (on day 10) equal numbers of animals from each group were studied on the hole-board for one hour following administration of either 1 ml/kg saline or 4 mg/kg DL-amphetamine sulphate.

TABLE 7: Effects of chronic pretreatment with 1 ml/kg saline or 1 mg/kg haloperidol for 11 days (days 1-10) on the response to acute administration of 1 ml/kg saline or 4 mg/kg DL-amphetamine sulphate (on day 12). The figures represent the behavioural response on the hole-board apparatus of each rat over a one hour period after injection.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

PRE-TREATMENT	ACTIVITY	RAT NO.						MEAN ± SEM
		1	2	3	4	5	6	
Chronic Saline Pretreatment + Saline 1.0 ml/kg	S	110	150	110	89	112	134	117 ± 9
	E	203	299	216	198	260	160	223 ± 20
	T	313	449	326	287	372	294	350 ± 62
	S/T	0.35	0.33	0.34	0.31	0.30	0.46	0.35 ± 0.02
	LOC	148	491	411	259	340	-	330 ± 59
Chronic Haloperidol Pretreatment + Saline 1.0 ml/kg	S	151	144	155	147	129	113	140 ± 7
	E	198	146	253	195	274	207	212 ± 18
	T	349	290	408	342	403	320	352 ± 18
	S/T	0.43	0.50	0.38	0.43	0.32	0.35	0.40 ± 0.02
	LOC	503	213	297	310	391	255	328 ± 43
Chronic Saline Pretreatment +Amphetamine 4 mg/kg	S	555	782	131	70	685	94	387 ± 131
	E	542	474	206	611	429	776	506 ± 78
	T	1097	1256	337	687	1114	870	893 ± 138
	S/T	0.51	0.62	0.39	0.11	0.61	0.11	0.39 ± 0.10
	LOC	638	-	399	626	441	431	507 ± 51
Chronic Haloperidol Pretreatment +Amphetamine 4 mg/kg	S	1022	1253	571	438	751	147	697 ± 163
	E	847	761	661	954	430	571	704 ± 78
	T	1869	2014	1232	1392	1181	718	1401 ± 195
	S/T	0.55	0.62	0.46	0.31	0.64	0.20	0.46 ± 0.07
	LOC	963	-	465	827	527	504	657 ± 97

None of the differences was statistically significant between the two groups which received acute saline treatment or between the groups which received acute amphetamine treatment (Mann-Whitney U test)

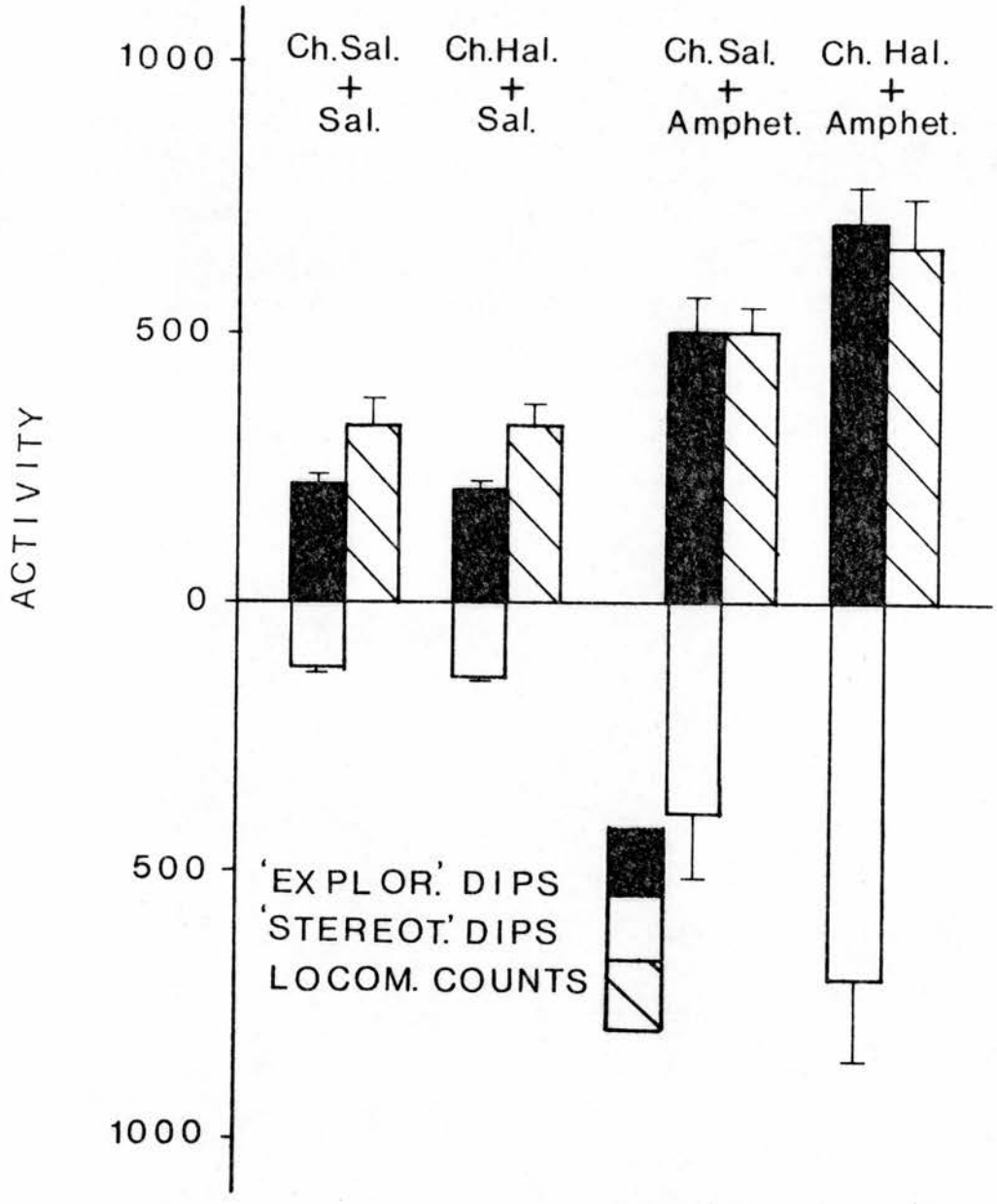


FIG. 22: Effects of chronic pretreatment with 1 ml/kg saline or 1 mg/kg haloperidol daily on the response to acute administration of 1 ml/kg saline or 4 mg/kg DL-amphetamine sulphate. The chronic pretreatments consisted of daily injections for 10 days (days 1-10). 48 hours later (day 12) the animals were given either 1 ml/kg or 4 mg/kg DL-amphetamine sulphate and behaviour recorded in the hole-board apparatus for one hour. There were six animals in each of the four groups. Each column represents mean activity ± S.E.M. during the entire one hour period.

During the course of haloperidol-treatment the injections on days 1-2 produced marked long-lasting (up to 24 hours) sedation. The final two or three injections no longer produced such a sedative effect, indicating the development of tolerance to the haloperidol. Instead the animals were noted to be irritable.

As in the previous experiment employing a dosage of 1 mg/kg haloperidol there was no difference in the behavioural response to saline administration between the two groups of rats (Fig.23, Table 8). There was however a marked difference between the two groups in the response to 4 mg/kg DL-amphetamine (Fig.23, Table 8). Compared with the "chronic saline" group, the "chronic haloperidol" group showed a marked increase in "stereotyped" dipping ($p \simeq 0.016$) and smaller increase in "exploratory" dipping (not statistically significant) so that the S/T ratio was increased ($p = 0.032$). Locomotor counts were also increased but this increase was not statistically significant.

(5) Effect of pretreatment with phenoxybenzamine hydrochloride 20 mg/kg on the response to 4 mg/kg DL-amphetamine sulphate

Animals were pretreated with 20 mg/kg phenoxybenzamine hydrochloride 40 minutes before an injection of 4 mg/kg DL-amphetamine sulphate following which they were studied for two hours on the hole-board. The results were compared with those animals in experiment 1 which were treated with 4 mg/kg DL-amphetamine sulphate only.

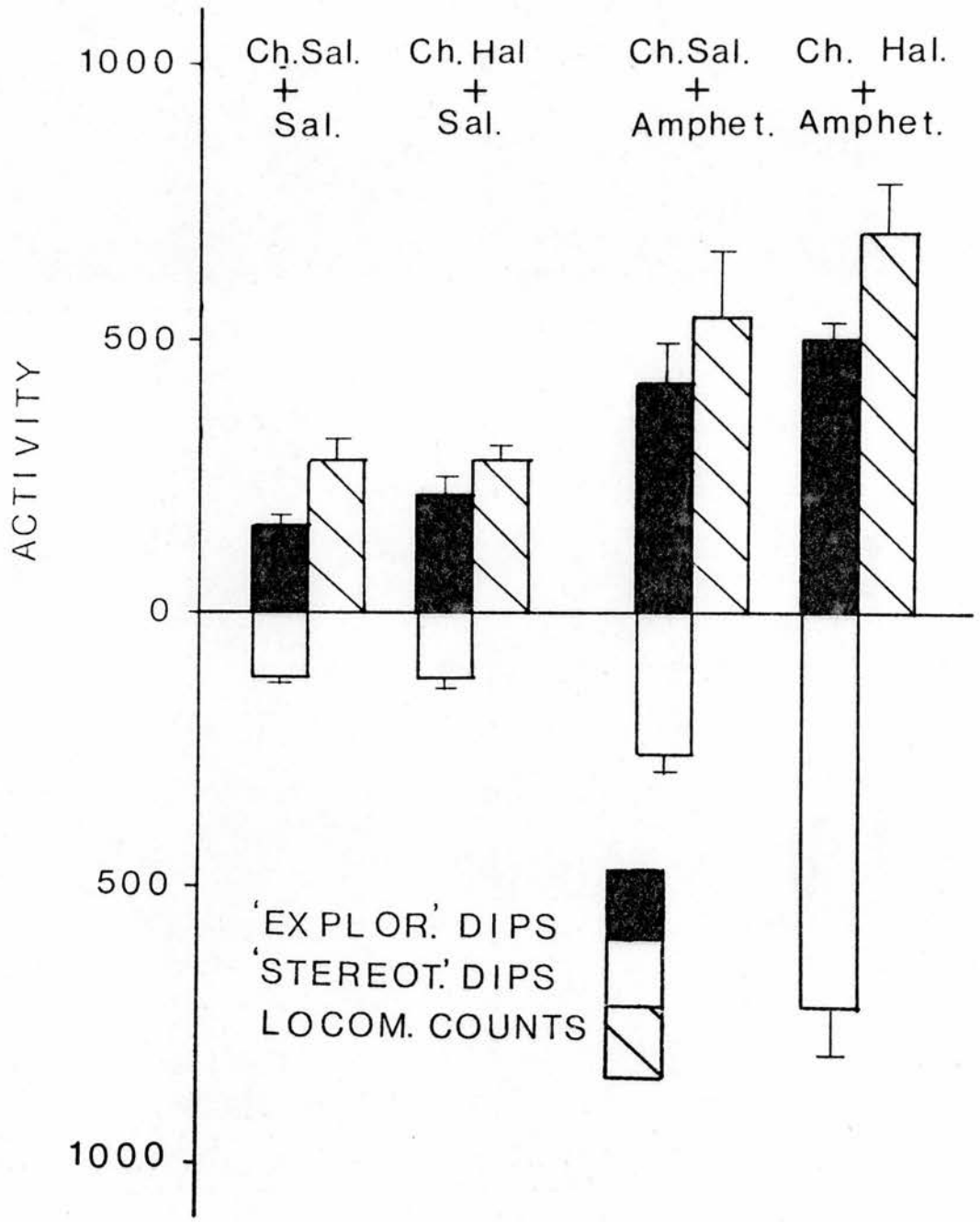


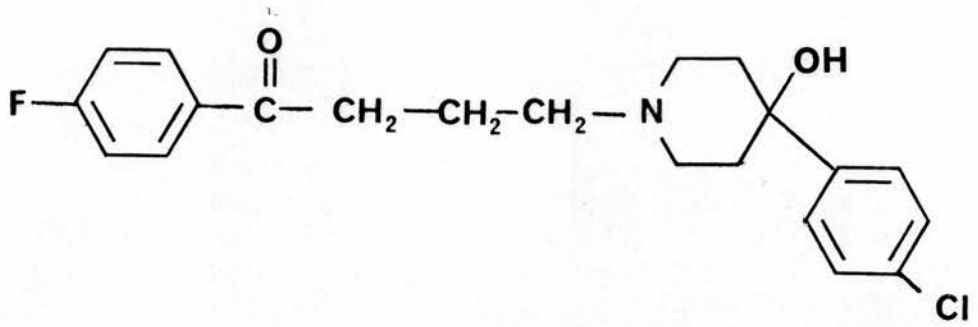
FIG. 23: Effects of chronic pretreatment with 1 ml/kg saline or 5 mg/kg haloperidol daily on the response to acute administration of 1 ml/kg saline or 4 mg/kg DL-amphetamine sulphate. The chronic pretreatments consisted of daily injections for 6 days (days 1-6). 4 days later (day 10) the animals were given either 1 ml/kg or 4 mg/kg DL-amphetamine sulphate and behaviour recorded in the hole-board apparatus for one hour. There were five animals in each of the four groups. Each column represents mean activity ± S.E.M. during the entire one hour period.

TABLE 8: Effects of chronic pretreatment with 1 ml/kg saline or 5 mg/kg haloperidol for 6 days (days 1-6) on the response to acute administration of 1 ml/kg saline or 4 mg/kg DL-amphetamine sulphate (on day 10). The figures represent the behavioural response on the hole-board apparatus of each rat over a one hour period after injection.

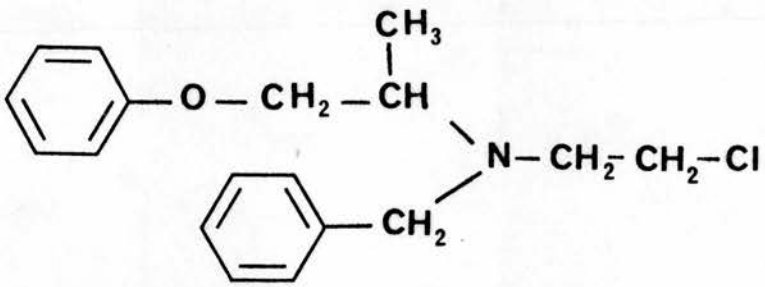
S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

PRETREATMENT	ACTIVITY	RAT NO.					MEAN ± SEM
		1	2	3	4	5	
Chronic Saline Pretreatment + Saline 1.0 ml/kg	S	94	125	78	159	134	118 ± 15
	E	99	125	177	217	165	157 ± 20
	T	193	250	255	376	299	275 ± 30
	S/T	0.49	0.50	0.31	0.42	0.45	0.43 ± 0.03
	LOC	86	189	322	282	256	277 ± 40
Chronic Haloperidol Pretreatment + Saline 1.0 ml/kg	S	187	42	78	158	141	121 ± 27
	E	281	78	181	299	236	215 ± 40
	T	468	120	259	457	377	336 ± 66
	S/T	0.40	0.35	0.30	0.35	0.37	0.35 ± 0.01
	LOC	360	236	208	274	326	281 ± 28
Chronic Saline Pretreatment + Amphetamine 4 mg/kg	S	253	230	160	384	276	261 ± 37
	E	323	238	264	593	618	407 ± 83
	T	576	468	424	977	894	668 ± 113
	S/T	0.44	0.49	0.38	0.39	0.31	0.40 ± 0.03
	LOC	463	260	352	571	1068	543 ± 141
Chronic Haloperidol Pretreatment + Amphetamine 4 mg/kg	S	802	718	949	357	748	*715 ± 98
	E	597	552	440	468	435	498 ± 34
	T	1399	1270	1384	825	1183	1213 ± 105
	S/T	0.57	0.57	0.68	0.43	0.63	**0.58 ± 0.04
	LOC	1027	818	599	481	524	690 ± 103

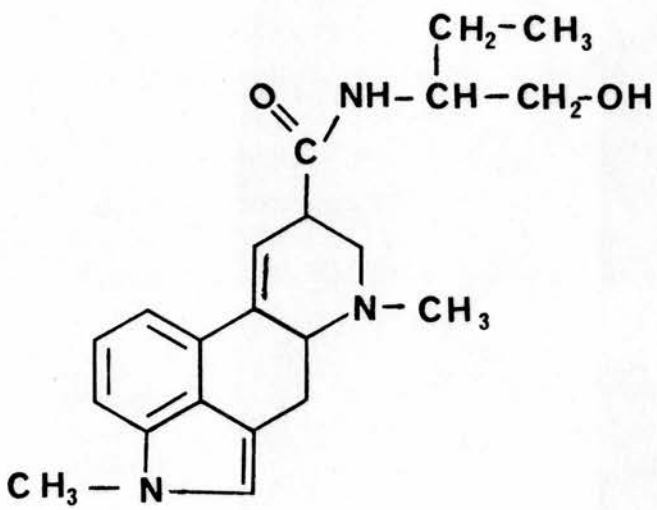
* p = 0.016
** p = 0.032
(Mann-Whitney U test - differences between the two amphetamine treated groups)



Haloperidol



Phenoxybenzamine



Methysergide

FIG. 24

Phenoxybenzamine alone tended to make the animals lethargic, sedated and ill-looking. Following amphetamine injection the initial exploratory response during the first 10 min. was markedly reduced compared to that of control animals receiving amphetamine only (Mann-Whitney U-test, $p = 0.002$ for "exploratory" dips, $p = 0.002$ for locomotor counts) and the behavioural response to the amphetamine somewhat delayed (Fig.25,26, Tables 9,10). There was no significant difference in the overall "stereotyped" dipping response between phenoxybenzamine pretreated and non-pretreated animals during the two hour period of testing. "Exploratory" dipping and locomotor counts were reduced ($p = 0.008$, N.S. respectively) whereas S/T ratio was increased ($p = 0.034$).

(6) Effect of pretreatment with methysergide 2 mg/kg on response to 4 mg/kg DL-amphetamine sulphate

Animals were pretreated with 2 mg/kg methysergide hydrogen maleinate 40 min. before administration of 4 mg/kg DL-amphetamine sulphate, following which they were studied for 2 hours on the hole-board.

There was an overall trend towards an increase in response to amphetamine in methysergide pretreated rats compared to non-pretreated rats (Figs. 25,26, Tables 9,10). Both "stereotyped" and "exploratory" dips were increased, as was locomotor response and S/T ratio. None of these differences achieved statistical significance.

(7) Response to Apomorphine Hydrochloride

Animals were studied on the hole-board for two hours immediately following intraperitoneal administration of 0.75, 1.5 or 3.0 mg/kg apomorphine hydrochloride.

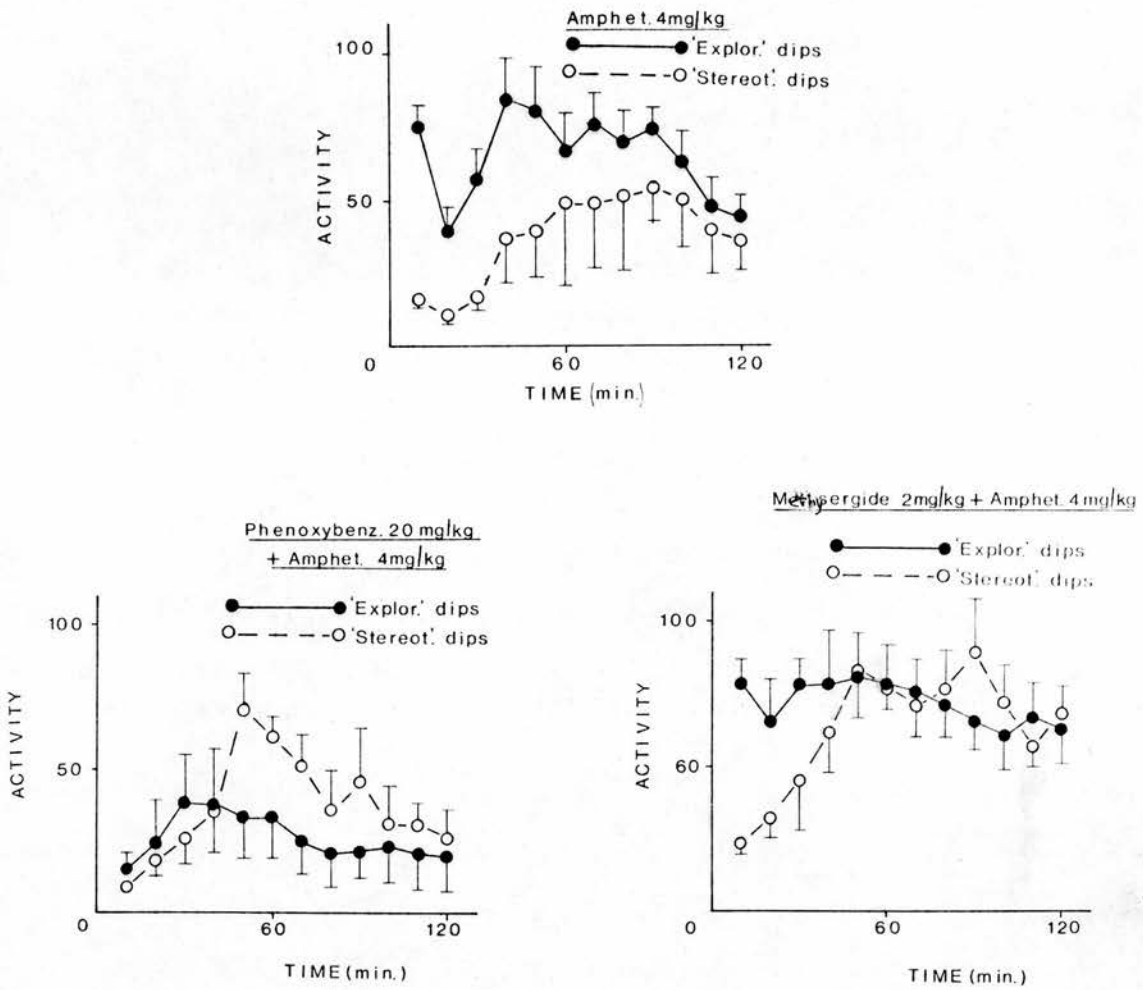


FIG. 25: Effects of pretreatment with 20 mg/kg phenoxybenzamine hydrochloride i.p. or 2 mg/kg methysergide hydrogen maleinate i.p. 40 min. before on the response to i.p. administration of 4 mg/kg DL-amphetamine sulphate in the hole-board. Each point represents mean activity ± S.E.M. of 6 or 7 rats during successive 10 min. intervals.

TABLE 9: Effects of pretreatment with 20 mg/kg phenoxybenzamine hydrochloride or 2.0 mg/kg methysergide hydrogen maleinate 40 min. before on the behavioural response to 4 mg/kg DL-amphetamine sulphate in the hole-board apparatus. Figures denote mean activity ± S.E.M. during successive 10 min. intervals after the amphetamine injection. The results for the two pretreatments are compared with the effects of amphetamine with no pretreatment. Six or seven animals were studied after each treatment.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts.

Fuller versions of this table, giving the responses of individual rats, can be found in the Appendix. (Tables 1, 5, 6).

TIME INTERVAL (min)	0 - 10			10 - 20		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	16 ± 3	75 ± 9	64 ± 8	11 ± 3	39 ± 8	36 ± 6
Phenoxybenzamine 20 mg/kg	8 ± 2	15 ± 6	24 ± 8	18 ± 8	24 ± 10	27 ± 12
Methysergide 2.0 mg/kg	23 ± 5	78 ± 10	90 ± 11	32 ± 8	66 ± 16	70 ± 15
TIME INTERVAL (min)	20 - 30			30 - 40		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	17 ± 4	57 ± 11	62 ± 10	37 ± 17	84 ± 15	52 ± 9
Phenoxybenzamine 20 mg/kg	26 ± 12	38 ± 16	34 ± 9	35 ± 12	37 ± 17	41 ± 12
Methysergide 2.0 mg/kg	45 ± 10	78 ± 18	79 ± 13	62 ± 15	78 ± 21	76 ± 19
TIME INTERVAL (min)	40 - 50			50 - 60		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	39 ± 17	81 ± 18	44 ± 12	48 ± 31	67 ± 14	53 ± 6
Phenoxybenzamine 20 mg/kg	70 ± 28	33 ± 13	35 ± 12	61 ± 25	33 ± 9	39 ± 11
Methysergide 2.0 mg/kg	83 ± 14	81 ± 16	76 ± 16	77 ± 8	78 ± 15	78 ± 22

(Contd.)

TABLE 9: continued

TIME INTERVAL (min)	60 - 70			70 - 80		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	49 ± 24	76 ± 12	51 ± 5	51 ± 27	70 ± 12	57 ± 7
Phenoxybenzamine 20 mg/kg	51 ± 22	24 ± 6	36 ± 11	35 ± 18	20 ± 8	34 ± 10
Methysergide 2.0 mg/kg	71 ± 12	76 ± 12	74 ± 16	77 ± 15	71 ± 12	80 ± 15
TIME INTERVAL (min)	80 - 90			90 - 100		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	53 ± 18	74 ± 9	55 ± 8	50 ± 18	63 ± 12	51 ± 17
Phenoxybenzamine 20 mg/kg	44 ± 21	21 ± 4	32 ± 10	31 ± 13	23 ± 8	38 ± 9
Methysergide 2.0 mg/kg	89 ± 21	65 ± 10	61 ± 10	72 ± 14	61 ± 13	68 ± 11
TIME INTERVAL (min)	100 - 110			100 - 120		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	39 ± 16	41 ± 11	48 ± 17	36 ± 11	44 ± 9	51 ± 21
Phenoxybenzamine 20 mg/kg	30 ± 12	20 ± 9	35 ± 12	26 ± 10	19 ± 9	36 ± 9
Methysergide 2.0 mg/kg	57 ± 9	67 ± 13	72 ± 15	68 ± 11	63 ± 13	77 ± 11

TABLE 10: Effects of pretreatment with 20 mg/kg phenoxybenzamine hydrochloride or 2.0 mg/kg methysergide hydrogen maleinate 40 min. before on the overall response to 4 mg/kg DL-amphetamine sulphate in the hole-board apparatus. Figures show the response of each animal over a two hour period following the amphetamine injection.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

PRETREATMENT	ACT-IVITY	RAT NO. 1	2	3	4	5	6	7	MEAN ± SEM
0	S	163	242	1306	366	228	374		446 ± 175
	E	862	771	518	566	862	1098		779 ± 88
	T	1025	1013	1824	932	1090	1472		1226 ± 142
	S/T	0.16	0.24	0.72	0.39	0.21	0.25		0.33 ± 0.08
	LOC	894	509	759	497	-	467		625 ± 83
Phenoxy-benzamine 20 mg/kg	S	378	933	131	1015	136	48	400	434 ± 148
	E	280	840	162	327	369	53	125	** 308 ± 99
	T	658	1773	293	1342	505	101	525	742 ± 226
	S/T	0.57	0.53	0.45	0.76	0.27	0.48	0.76	* 0.55 ± 0.07
	LOC	380	717	361	362	792	54	224	413 ± 98
Methysergide 2.0 mg/kg	S	932	916	782	1031	322	705	602	756 ± 91
	E	1529	787	1136	555	923	418	693	863 ± 143
	T	2461	1703	1918	1586	1245	1123	1295	1619 ± 176
	S/T	0.38	0.54	0.41	0.65	0.26	0.63	0.46	0.48 ± 0.05
	LOC	952	884	1195	585	1554	597	540	901 ± 141

** $p = 0.008$
* $p = 0.034$

(Mann-Whitney U test)

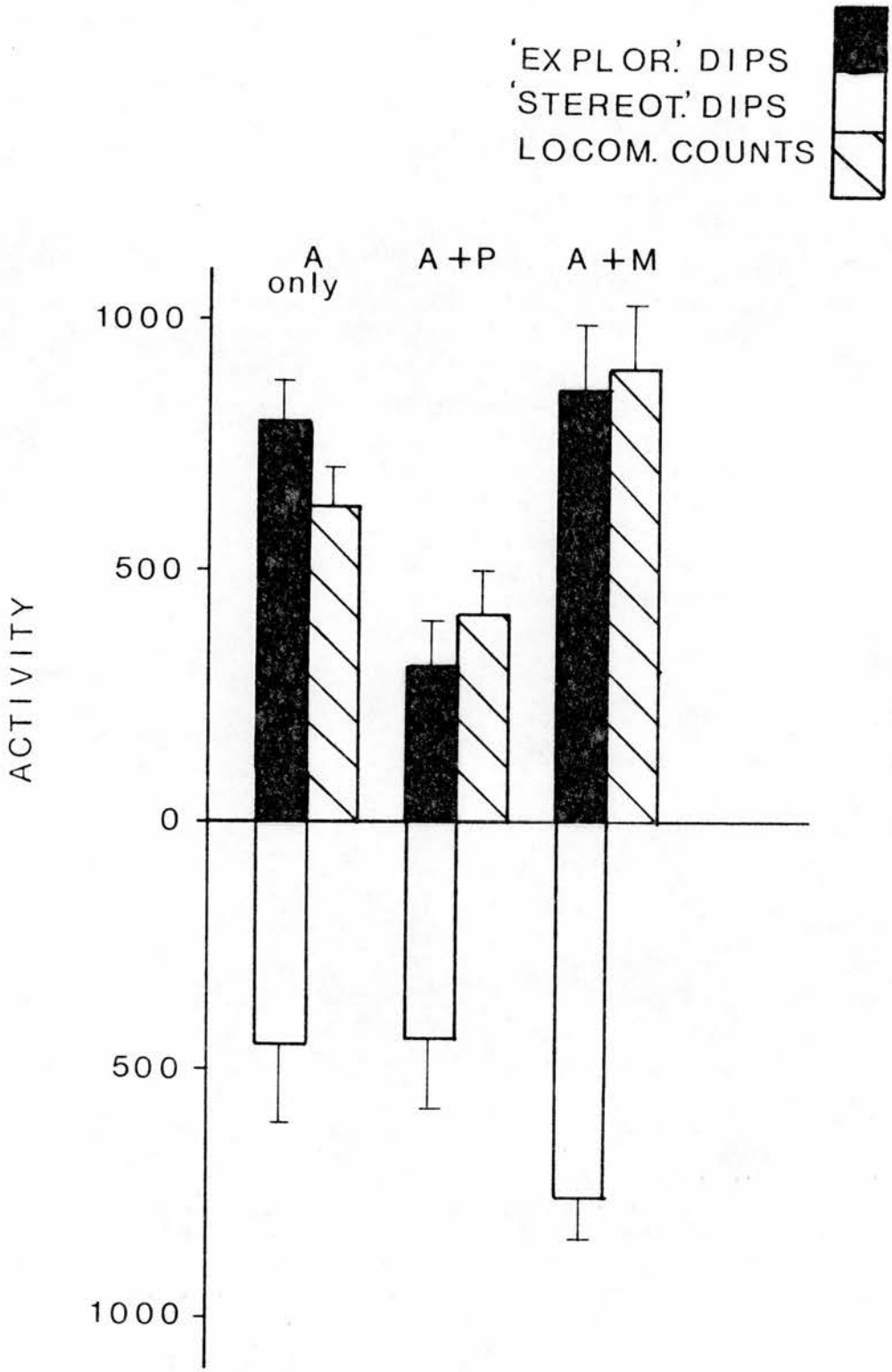


FIG. 26: Effects of pretreatment with 20 mg/kg phenoxybenzamine hydrochloride i.p. or 2 mg/kg methysergide hydrogen maleinate i.p. 40 min. before on the overall response to i.p. administration of 4 mg/kg DL-amphetamine sulphate during a 2 hour period. Each column represents mean response ± S.E.M. of 6 or 7 rats during the two-hour period immediately after the amphetamine injection.

A - Amphetamine; P - Phenoxybenzamine; M - Methysergide

The behavioural actions of apomorphine were noticeable within two minutes of injection and wore off after 40 - 50 minutes (Fig.27). Hole-dipping was inhibited and the initial burst of "exploratory" dipping was also greatly reduced (Figs. 27,28, Tables 11,12). The reduction in dipping behaviour which affected both types of dipping appeared dose-related. Locomotor counts were less affected.

Behaviour under the influence of apomorphine had a distinctive pattern. With the lowest doses, (0.75 mg and 1.5 mg/kg) animals crawled slowly from hole to hole, sniffing between and around the holes. At the higher doses (1.5 and 3.0 mg/kg) the animals spent more and more time at each hole, moving around less. Intense sniffing took place around the hole, and in due course characteristic biting movements were observed, the animal repeatedly thrusting its jaws around the hole edge and snapping them shut. This pattern of responses was identical to that seen in a previous study (Makanjuola, 1976, Makanjuola et al. 1977b).

Analysis of the results showed that for the overall response during the entire two-hour observation period only the decreases in stereotyped dipping with increased dosage of apomorphine were statistically significant ($p < 0.05$). During each of the first four 10 min. periods, statistically significant differences were found for other parameters (Table 11).

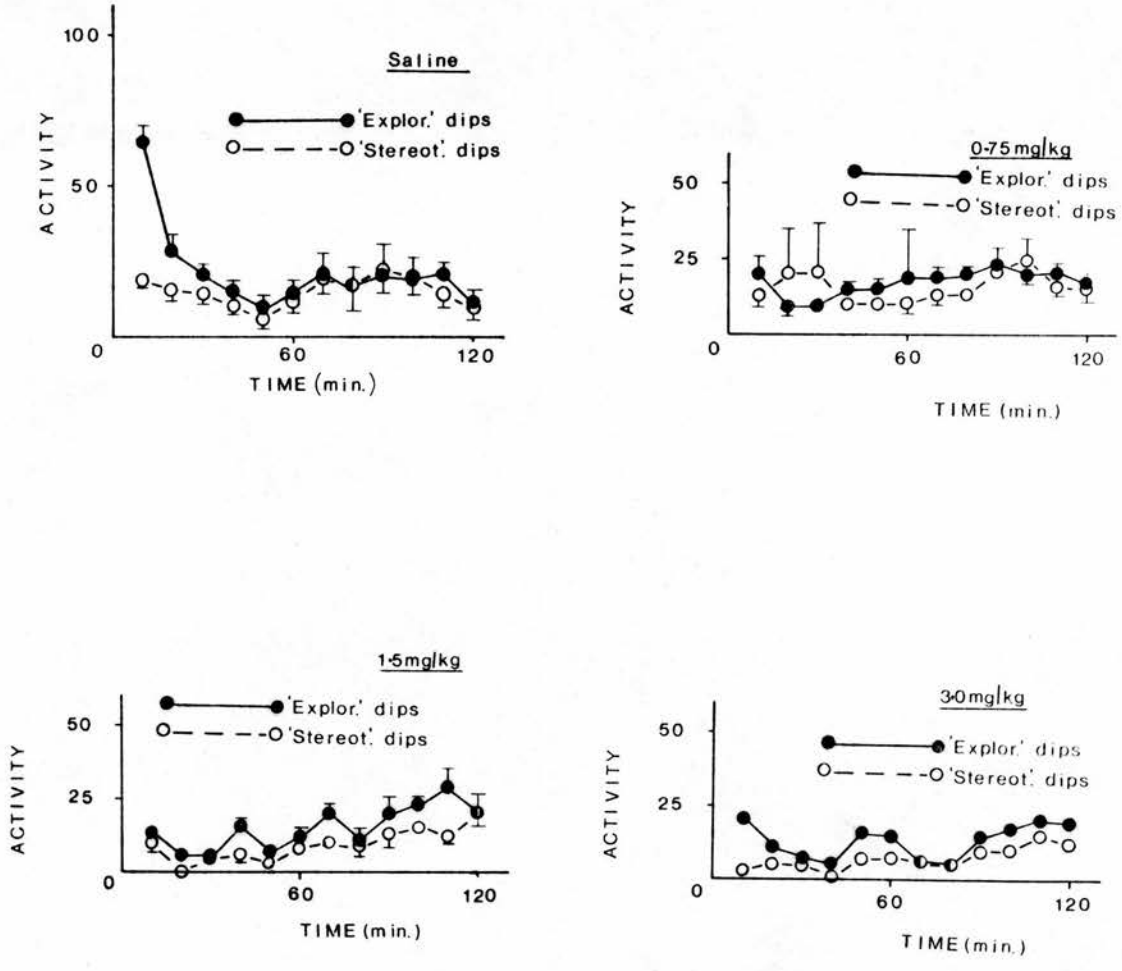


FIG. 27: Behavioural response in the hole-board apparatus following i.p. administration of 1 ml/kg saline or 0.75, 1.5 or 3.0 mg/kg apomorphine hydrochloride. Each point represents mean response ± S.E.M. of 6 or 7 rats during successive 10 min. intervals following the injection.

TABLE 11: Behaviour of rats in the hole-board apparatus following administration of 1 ml/kg saline or 0.75, 1.5 or 3.0 mg/kg apomorphine hydrochloride i.p. Figures show mean activity ± S.E.M. during successive 10 min. intervals after injection. Six or seven animals were studied at each dose level.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts.

Details of the responses of individual rats can be found in the Appendix (Tables 1, 7-9).

TIME INTERVAL (min)	0 - 10			10 - 20		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	18 ± 2	64 ± 5	48 ± 5	16 ± 4	28 ± 7	31 ± 7
0.75	13 ± 5	20 ± 6	27 ± 9	21 ± 15	8 ± 4	25 ± 10
1.5	9 ± 4	13 ± 2	28 ± 3	0.4 ± 0.3	6 ± 2	23 ± 6
3.0	3 ± 2 *	21 ± 7 **	31 ± 8	5 ± 4 **	11 ± 5 *	27 ± 9
TIME INTERVAL (min)	20 - 30			30 - 40		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	14 ± 4	21 ± 4	30 ± 7	10 ± 3	15 ± 4	18 ± 7
0.75	21 ± 17	8 ± 2	8 ± 5	9 ± 2	14 ± 3	19 ± 9
1.5	4 ± 2	6 ± 1	33 ± 8	6 ± 3	16 ± 3	21 ± 6
3.0	4 ± 2	7 ± 5 *	23 ± 13	1 ± 1	5 ± 3	48 ± 13
TIME INTERVAL (min)	40 - 50			50 - 60		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	6 ± 3	10 ± 4	9 ± 4	12 ± 4	13 ± 4	14 ± 5
0.75	9 ± 2	15 ± 4	16 ± 5	10 ± 4	18 ± 8	31 ± 15
1.5	3 ± 1	7 ± 1	16 ± 5	8 ± 2	12 ± 4	17 ± 8
3.0	7 ± 2	16 ± 3	28 ± 8	7 ± 2	14 ± 4	27 ± 3

* p 0.05
** p 0.01

(Kruskal-Wallis one-way analysis of variance)

(Contd.)

TABLE 11: Continued

TIME INTERVAL (min)	60 - 70			70 - 80		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	19 ± 5	21 ± 8	19 ± 5	17 ± 10	17 ± 5	12 ± 4
0.75	13 ± 5	18 ± 5	14 ± 8	13 ± 2	20 ± 3	29 ± 14
1.5	10 ± 2	20 ± 4	19 ± 4	8 ± 5	11 ± 5	16 ± 10
3.0	6 ± 2	7 ± 3	7 ± 4	5 ± 2	6 ± 3	10 ± 7
TIME INTERVAL (min)	80 - 90			90 - 100		
DOSE (mg/kg	S	E	LOC	S	E	LOC
0	22 ± 8	20 ± 7	16 ± 4	20 ± 5	18 ± 6	17 ± 4
0.75	21 ± 2	23 ± 6	32 ± 9	24 ± 9	19 ± 4	32 ± 19
1.5	13 ± 5	20 ± 6	14 ± 5	15 ± 2	23 ± 3	10 ± 1
3.0	9 ± 4	14 ± 5	16 ± 8	10 ± 3	17 ± 4	20 ± 4
TIME INTERVAL (min)	100 - 110			110 - 120		
DOSE (mg/kg	S	E	LOC	S	E	LOC
0	14 ± 4	21 ± 5	18 ± 5	10 ± 4	12 ± 4	12 ± 7
0.75	16 ± 5	20 ± 5	22 ± 14	15 ± 4	17 ± 6	14 ± 6
1.5	12 ± 3	29 ± 7	20 ± 4	21 ± 8	21 ± 6	29 ± 8
3.0	14 ± 4	20 ± 8	15 ± 8	12 ± 3	19 ± 3	22 ± 7

TABLE 12: Overall behavioural response in the hole-board apparatus during a two hour period following administration of 1 ml/kg saline or 0.75, 1.5 or 3.0 mg/kg apomorphine hydrochloride i.p. Figures show the response of each of a group of six or seven animals under any one treatment. A total of 26 animals were employed.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

DOSE (mg/kg)	ACTIVITY	RAT NO.							MEAN ± SEM
		1	2	3	4	5	6	7	
0	S	132	107	239	246	211	141		179 ± 24
	E	265	191	274	350	307	178		261 ± 26
	T	397	298	513	596	518	319		449 ± 49
	S/T	0.33	0.36	0.47	0.41	0.41	0.44		0.40±0.02
	LOC	287	150	211	386	187	284		251 ± 35
0.75	S	87	344	202	167	275	107	127	187 ± 36
	E	188	117	165	164	402	193	171	200 ± 35
	T	275	461	367	331	677	300	298	387 ± 54
	S/T	0.32	0.75	0.55	0.50	0.41	0.36	0.42	0.47±0.05
	LOC	271	222	-	-	440	187	414	307 ± 51
1.5	S	151	43	159	188	45	138	56	111 ± 23
	E	271	71	182	181	150	261	140	179 ± 26
	T	422	114	341	369	195	399	196	290 ± 45
	S/T	0.36	0.38	0.47	0.51	0.23	0.35	0.29	0.37±0.04
	LOC	434	210	154	234	186	-	-	244± 49
3.0	S	93	122	18	92	79	95		83 ± 14
	E	191	273	88	167	149	80		158 ± 28
	T	284	395	106	259	228	175		241 ± 41
	S/T	0.33	0.31	0.17	0.36	0.35	0.54		0.34±0.05
	LOC	524	197	-	265	225	226		287 ± 66

Kruskal-Wallis one-way analysis of variance: $p < 0.05$ for "stereotyped" dips.

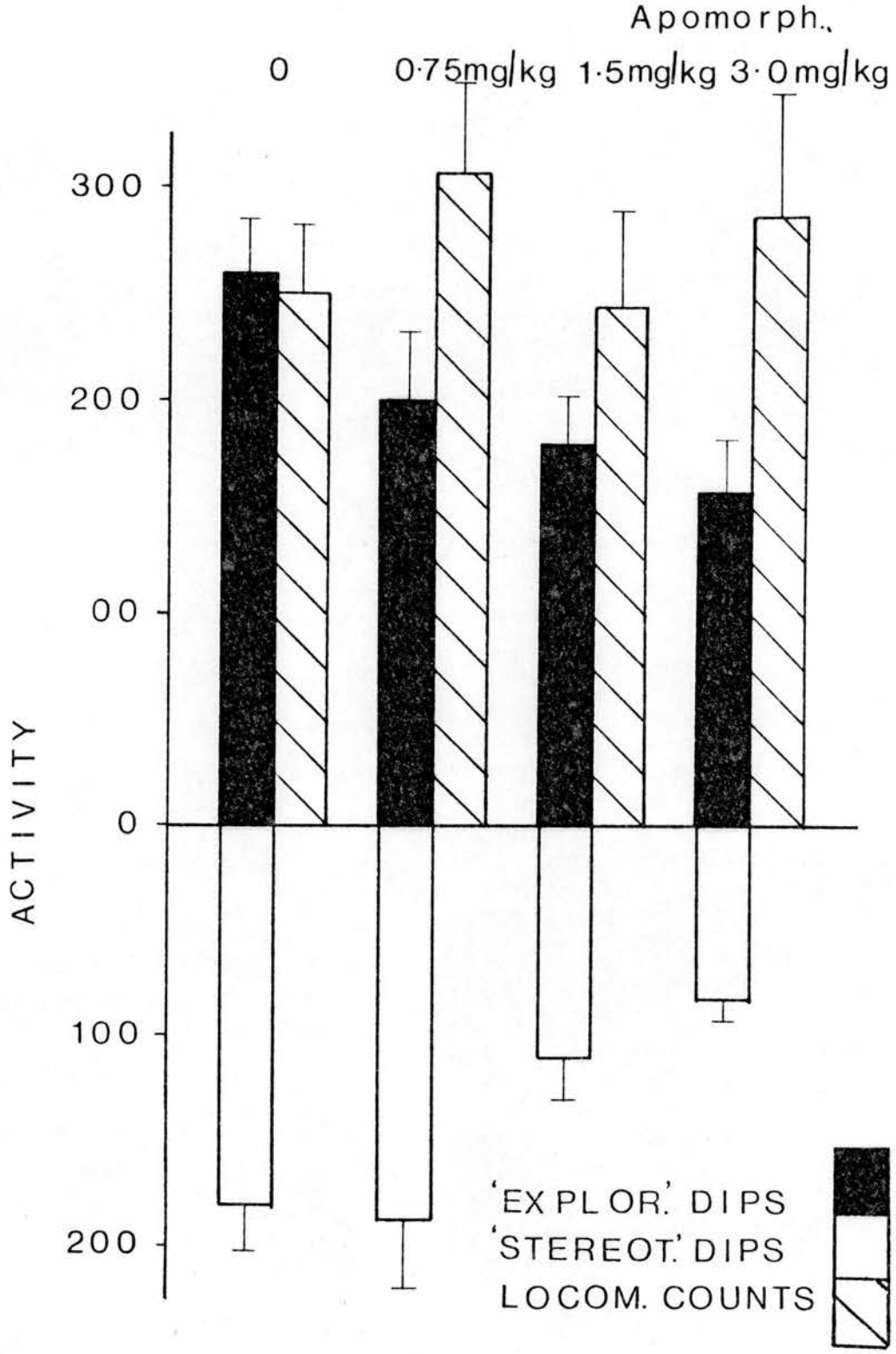


FIG. 28: Overall behavioural response in the hole-board apparatus following i.p. administration of 1 ml/kg saline (dose 0) or 0.75, 1.5 or 3.0 mg/kg apomorphine hydrochloride. Each column represents mean activity ± S.E.M. for the entire 2 hour period after injection.

(8) Effects of 5-Methoxy,N,N-Dimethyl Tryptamine

Animals were studied on the hole-board for two hours immediately following intraperitoneal administration of 2.5, 5 or 10 mg/kg 5-methoxy - N,N-dimethyltryptamine.

This drug produced a rather bizarre behavioural pattern which intensified with increasing dosage. Onset of the response was within two minutes and the response to the drug wore off within 35 - 50 minutes, the higher doses acting for slightly longer than the lower ones. The normal initial burst of exploratory dipping was interrupted, and therefore reduced, by the onset of the drug-induced behaviour (Fig.29 ,Tables 13,14). The animal assumed a very flattened posture as it crawled slowly round from hole to hole. Occasionally brief kyphotic posturing was also seen. While crawling around, all four limbs scrabbled in an incoordinated fashion on the floor of the hole-board. This incoordination was more obvious with the hind limbs so that the animal appeared to move around by pulling itself forward by its fore limbs. The animal nodded its head repeatedly both at and between holes. In relation to a hole, characteristically the head would remain thrust down a hole for long periods, with the nodding continuing therein. Such changes in motor activity were not recordable by the apparatus and no striking changes were recorded for hole-dipping and locomotor activity compared with saline-treated animals, apart from the first ten minutes, when the initial burst of exploratory dipping normally seen in saline-treated

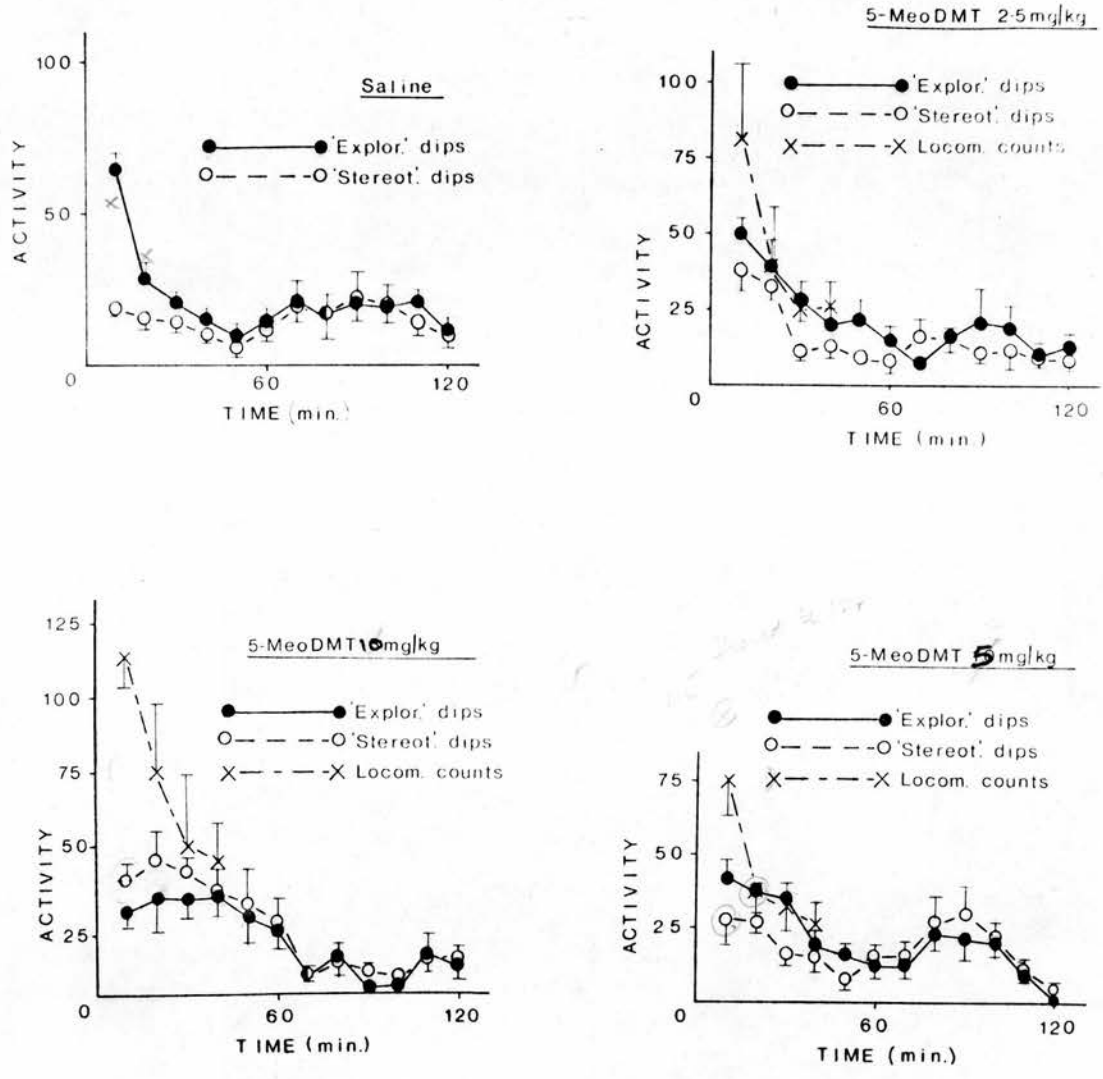


FIG. 29: Behavioural response in the hole-board apparatus following i.p. administration of 1 ml/kg saline or 2.5, 5 or 10 mg/kg 5-Methoxy-,N.N.-dimethyltryptamine (5-MEODMT). Each point represents mean activity ± S.E.M. during successive 10 min. intervals after injection. Locomotor counts are depicted for the first four 10 min. intervals only in the 5-MEODMT treated animals.

TABLE 13: Recorded behaviour of rats in the hole-board apparatus following administration of 1 ml/kg saline or 2.5, 5.0 or 10.0 mg/kg 5-methoxy-N N-Dimethyltryptamine i.p. Figures show mean activity ± S.E.M. during successive 10 min. intervals after injection. Four to six animals were studied at each dose level.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts

Details of the responses of individual rats can be found in the Appendix (Tables 1; 10-12).

TIME INTERVAL (min)	0 - 10			10 - 20		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	18 ± 2	64 ± 5	48 ± 5	16 ± 4	28 ± 7	31 ± 7
2.5	37 ± 7	50 ± 6	81 ± 25	32 ± 5	39 ± 11	38 ± 19
5.0	28 ± 10	42 ± 6	75 ± 12	27 ± 4	37 ± 4	38 ± 12
10.0	38 ± 7	28 ± 6 **	114 ± 10 **	45 ± 11	32 ± 12	75 ± 25
TIME INTERVAL (min)	20 - 30			30 - 40		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	14 ± 4	21 ± 4	30 ± 7	10 ± 3	15 ± 4	18 ± 7
2.5	11 ± 3	28 ± 7	25 ± 4	13 ± 5	20 ± 6	26 ± 8
5.0	16 ± 4	35 ± 6	32 ± 8	15 ± 6	19 ± 6	25 ± 7
10.0	41 ± 5	32 ± 7	50 ± 27	34 ± 9 *	33 ± 8	43 ± 13
TIME INTERVAL (min)	40 - 50			50 - 60		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	6 ± 3	10 ± 4	9 ± 4	12 ± 4	13 ± 4	14 ± 5
2.5	9 ± 2	22 ± 7	25 ± 8	8 ± 5	14 ± 5	30 ± 8
5.0	7 ± 4	16 ± 4	26 ± 8	15 ± 5	12 ± 4	16 ± 3
10.0	30 ± 13	26 ± 8	42 ± 19	24 ± 9	21 ± 7	28 ± 8

** $p < 0.02$
* $p < 0.05$

(Kruskal-Wallis one-way analysis of variance)

(Contd.)

TABLE 13: continued

TIME INTERVAL (min)	60 - 70			70 - 80		
DOSE (mg/kg	S	E	LOC	S	E	LOC
0	19 ± 5	21 ± 8	19 ± 5	17 ± 10	17 ± 5	12 ± 4
2.5	16 ± 7	7 ± 1	20 ± 15	15 ± 5	16 ± 3	15 ± 5
5.0	15 ± 6	12 ± 4	43 ± 18	26 ± 10	23 ± 6	21 ± 9
10.0	6 ± 2	6 ± 3	10 ± 4	10 ± 5	12 ± 6	22 ± 14
TIME INTERVAL (min)	80 - 90			90 - 100		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	22 ± 8	20 ± 7	16 ± 4	20 ± 5	18 ± 6	17 ± 4
2.5	10 ± 3	21 ± 13	30 ± 16	11 ± 7	19 ± 8	32 ± 16
5.0	30 ± 10	21 ± 8	23 ± 6	22 ± 5	20 ± 5	30 ± 10
10.0	7 ± 3	2 ± 2	2 ± 1	5 ± 2	2 ± 1	5 ± 4
TIME INTERVAL (min)	100 - 110			110 - 120		
DOSE (mg/kg)	S	E	LOC	S	E	LOC
0	14 ± 4	21 ± 5	18 ± 5	10 ± 4	12 ± 4	17 ± 7
2.5	9 ± 3	10 ± 4	39 ± 24	8 ± 3	13 ± 5	21 ± 9
5.0	10 ± 4	10 ± 4	15 ± 10	4 ± 3	1 ± 1	3 ± 2
10.0	12 ± 5	13 ± 8	22 ± 13	12 ± 4	9 ± 5	12 ± 8

TABLE 14: Overall recorded behavioural response in the hole-board apparatus during a 2-hour period following administration of 1 ml/kg saline or 2.5, 5.0 or 10.0 mg/kg 5, Methoxy,-N,N-Dimethyltryptamine i.p. Figures show the overall response of each of a group of 4-6 rats under any one treatment. 20 animals were employed.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

DOSE (mg/kg)	ACTIVITY	RAT NO.						MEAN ± SEM
		1	2	3	4	5	6	
0	S	132	107	239	246	211	141	179 ± 24
	E	265	191	274	350	307	178	261 ± 26
	T	397	298	513	596	518	319	440 ± 49
	S/T	0.33	0.36	0.47	0.41	0.41	0.44	0.40 ± 0.02
	LOC	287	150	211	386	187	284	251 ± 35
2.5	S	173	165	222	164			181 ± 13
	E	284	311	210	220			256 ± 23
	T	457	476	432	384			437 ± 19
	S/T	0.38	0.35	0.51	0.43			0.42 ± 0.03
	LOC	480	339	242	443			376 ± 50
5	S	380	139	142	182	207		210 ± 44
	E	262	152	270	178	359		244 ± 36
	T	642	291	412	360	566		348 ± 83
	S/T	0.59	0.48	0.34	0.51	0.37		0.46 ± 0.04
	LOC	314	150	572	191	515		348 ± 83
10	S	221	335	306	256	194		262 ± 25
	E	347	311	194	112	120		217 ± 47
	T	568	646	500	368	314		479 ± 60
	S/T	0.39	0.52	0.61	0.70	0.62		0.57 ± 0.05
	LOC	672	613	462	212	227		437 ± 93

None of the changes in behavioural parameters were statistically significant (Kruskal-Wallis one-way analysis of variance).

rats was reduced (Fig.29), this being accompanied by an increase in locomotor counts caused by the hyperactivity.

(9) Effects of monoamine uptake inhibitors on behaviour and their interactions with DL-amphetamine

(a) Effects on spontaneous behaviour

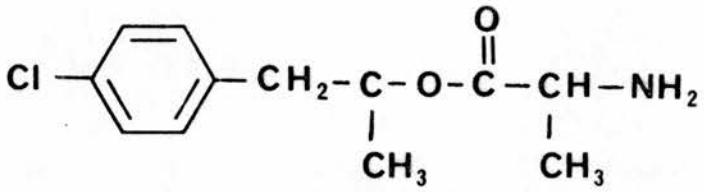
Desmethylimipramine hydrochloride 25 mg/kg), chlorimipramine hydrochloride (25 mg/kg) and GEA 654 (50 mg/kg) were administered i.p. 30 minutes before saline 1 ml/kg i.p., immediately whereupon the animals were placed on the hole-board. Benztropine (2.5 and 5.0 mg/kg) and LRCL 5182 (10 and 20 mg/kg) were not followed by saline injection, the animals being placed on the hole-board immediately after injection with the test drug. The results are compared with those from rats given saline alone.

Structural formulae of these compounds are shown in Figs. 5 and 30. GEA 654 and LRCL 5182 are selective inhibitors of 5-HT and dopamine uptake respectively (see page 189).

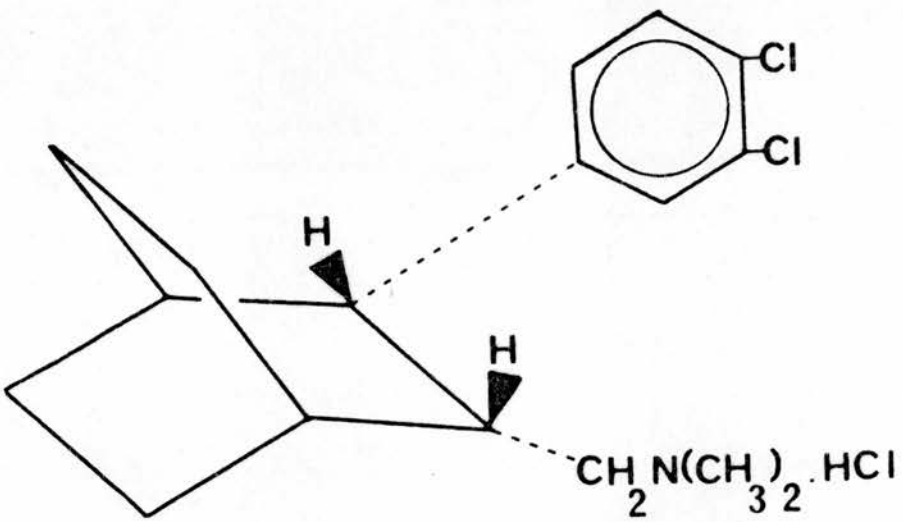
Desmethylimipramine (DMI) (Figs.31b,33, Tables 15,16) produced a reduction in all forms of activity on the hole-board. The initial burst of exploratory dipping and locomotion appeared reduced compared with non-pretreated rats but these reductions were not statistically significant.

Thereafter the subsequent level of all activity was also reduced in comparison with animals given saline only. (For the overall response during the 2-hour period $p = 0.004$ for "stereotyped" dips, $p = 0.004$ for "exploratory" dips, $p = 0.016$ for locomotor counts.)

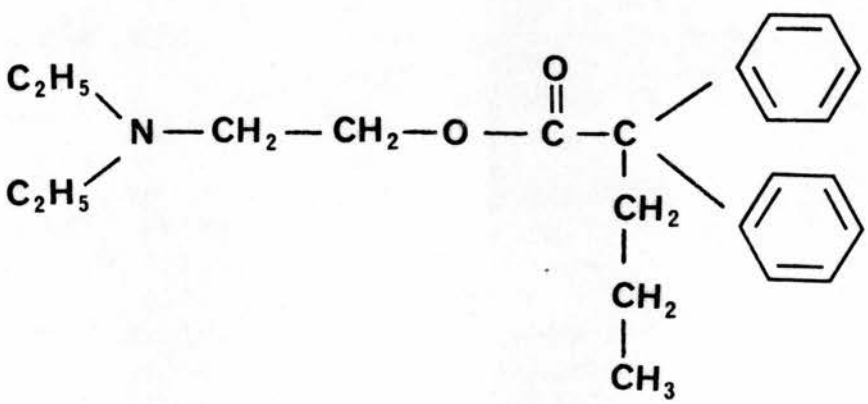
Chlorimipramine (CMI) produced only a slight reduction in activity which was not statistically significant. (Fig.31c, Tables 15,16).



GEA-654



LRCL 5182



SKF-525A

FIG. 30

TABLE 15: Effects of pretreatment with desmethylimipramine hydrochloride (DMI) 25 mg/kg chlorimipramine HCL (CMI) 25 mg/kg or "GEA 654" 50 mg/kg 30 min. before on the response to administration of 1 ml/kg saline in the hole-board apparatus. Figures show the mean activity ± S.E.M. during successive 10 min. intervals following the second injection. Six animals were studied with each treatment.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts.

Details of the responses of individual rats can be found in the Appendix (Tables 1; 13-15).

TIME INTERVAL (min)	0 - 10			10 - 20		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	18 ± 2	64 ± 5	48 ± 5	16 ± 4	28 ± 7	31 ± 7
DMI	10 ± 2	41 ± 7	46 ± 9	5 ± 1	12 ± 3	8 ± 2
CMI	20 ± 3	57 ± 10	39 ± 7	19 ± 4	27 ± 5	16 ± 4
GEA 654	19 ± 5	56 ± 13	39 ± 10	22 ± 7	40 ± 9	26 ± 3
TIME INTERVAL (min)	20 - 30			30 - 40		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	14 ± 4	21 ± 4	30 ± 7	10 ± 3	15 ± 4	18 ± 7
DMI	7 ± 2	12 ± 5	3 ± 1	7 ± 1	12 ± 5	8 ± 3
CMI	17 ± 4	13 ± 4	11 ± 2	16 ± 4	15 ± 3	7 ± 1
GEA 654	18 ± 3	28 ± 6	19 ± 3	23 ± 7	28 ± 7	11 ± 3
TIME INTERVAL (min)	40 - 50			50 - 60		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	6 ± 3	10 ± 4	9 ± 4	12 ± 4	13 ± 4	14 ± 5
DMI	7 ± 2	9 ± 4	6 ± 3	6 ± 1	10 ± 1	8 ± 1
CMI	12 ± 2	13 ± 2	6 ± 2	14 ± 3	14 ± 3	10 ± 8
GEA 654	19 ± 4	26 ± 5	51 ± 19	20 ± 3	35 ± 1	26 ± 6

(Contd.)

TABLE 15: continued

TIME INTERVAL (min)	60 - 70			70 - 80		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	19 ± 5	21 ± 8	19 ± 5	17 ± 10	17 ± 5	12 ± 4
DMI	4 ± 1	3 ± 1	8 ± 5	6 ± 3	2 ± 1	2 ± 1
CMI	12 ± 5	12 ± 3	14 ± 7	11 ± 5	14 ± 6	10 ± 6
GEA 654	16 ± 4	20 ± 6	20 ± 5	22 ± 7	26 ± 8	16 ± 6
TIME INTERVAL (min)	80 - 90			90 - 100		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	22 ± 8	20 ± 7	16 ± 4	20 ± 5	18 ± 6	17 ± 4
DMI	4 ± 2	3 ± 1	5 ± 2	4 ± 2	3 ± 2	2 ± 1
CMI	17 ± 3	25 ± 6	24 ± 9	11 ± 3	12 ± 5	10 ± 5
GEA 654	23 ± 10	27 ± 8	18 ± 5	13 ± 4	18 ± 7	11 ± 5
TIME INTERVAL (min)	100 - 110			110 - 120		
PRE-TREATMENT	S	E	LOC	S	E	LOC
0	14 ± 4	21 ± 5	18 ± 5	10 ± 4	12 ± 4	17 ± 7
DMI	4 ± 1	4 ± 1	7 ± 4	5 ± 2	7 ± 3	20 ± 12
CMI	9 ± 3	10 ± 5	5 ± 3	5 ± 2	6 ± 3	9 ± 7
GEA 654	22 ± 5	28 ± 8	23 ± 10	18 ± 6	13 ± 5	5 ± 2

TABLE 16: Effects of pretreatment with Desmethylimipramine HCL (DMI) 25 mg/kg, Chlorimipramine HCL (CMI) 25 mg/kg or "GEA 654" 50 mg/kg on the overall response to 1 ml/kg saline during a 2 hour period. Figures show the overall response of each of a group of 5 or 6 rats under any one treatment. 23 animals were employed.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

TREATMENT	ACTIVITY	RAT NO. 1	2	3	4	5	6	MEAN ± SEM
Saline 1 ml/kg only	S	132	107	239	246	211	141	179 ± 24
	E	265	191	274	350	307	178	261 ± 26
	T	397	298	513	596	518	319	440 ± 49
	S/T	0.33	0.36	0.47	0.41	0.41	0.44	0.40 ± 0.02
	LOC	287	150	211	386	187	284	251 ± 35
DMI 25 mg/kg + Saline 1 ml/kg	S	39	74	37	121	72	74	**69 ± 12
	E	43	182	101	90	131	160	**118 ± 21
	T	82	256	138	211	203	234	187 ± 26
	S/T	0.48	0.29	0.27	0.57	0.35	0.32	0.38 ± 0.05
	LOC	48	204	79	156	143	117	*124 ± 23
CMI 25 mg/kg + Saline 1 ml/kg	S	124	139	125	177	133	287	164 ± 26
	E	202	222	235	159	192	279	215 ± 16
	T	326	361	360	336	325	566	379 ± 38
	S/T	0.38	0.39	0.35	0.53	0.41	0.51	0.43 ± 0.03
	LOC	149	125	143	101	147	310	162 ± 31
GEA 654 50 mg/kg + Saline 1 ml/kg	S	197	68	291	242	378		235 ± 51
	E	382	137	385	485	335		345 ± 57
	T	579	205	676	727	713		580 ± 87
	S/T	0.34	0.33	0.43	0.33	0.53		0.39 ± 0.04
	LOC	331	250	345	284	165		275 ± 32

** p = 0.004
* p = 0.016

(Mann-Whitney U test)

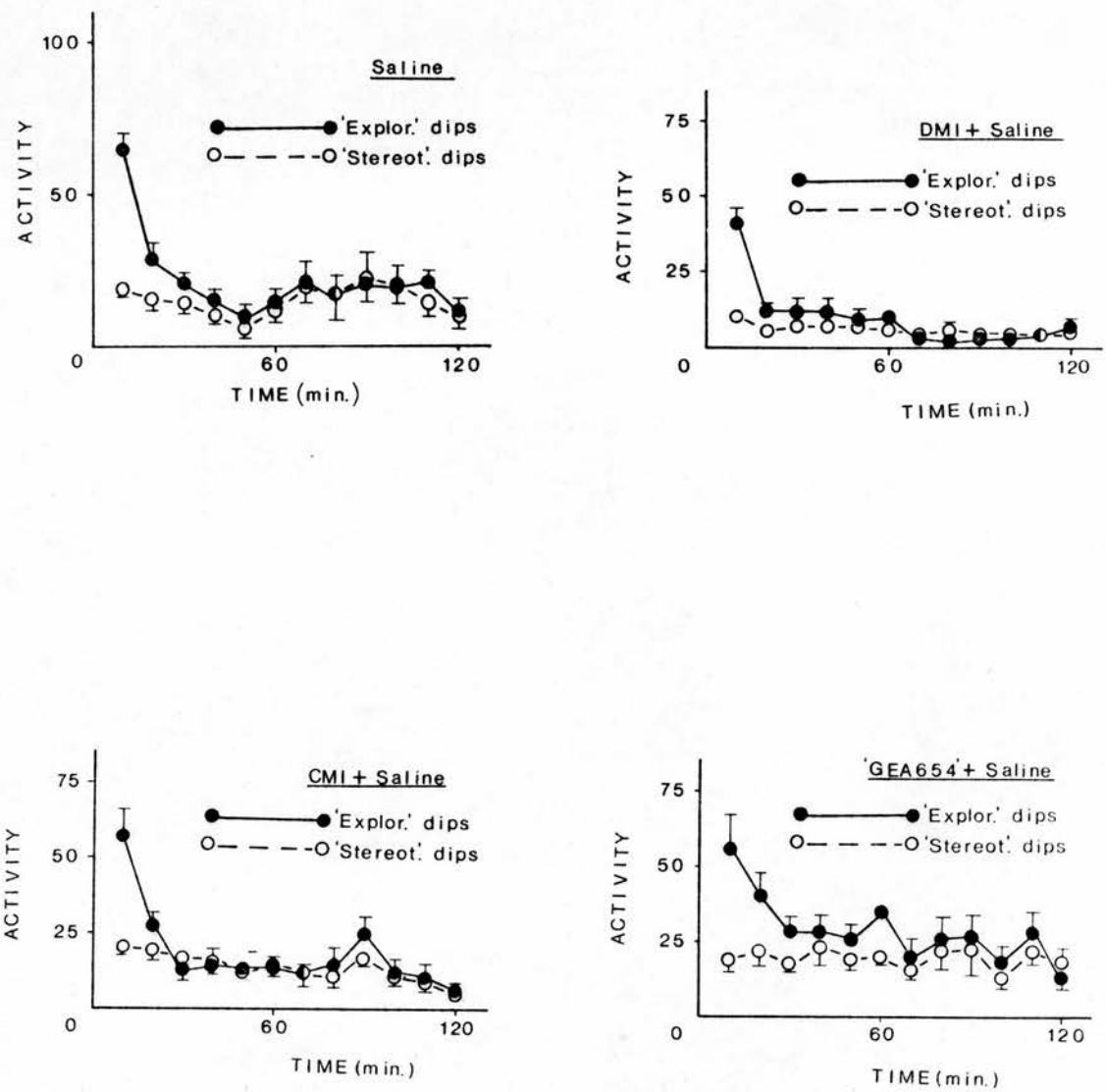
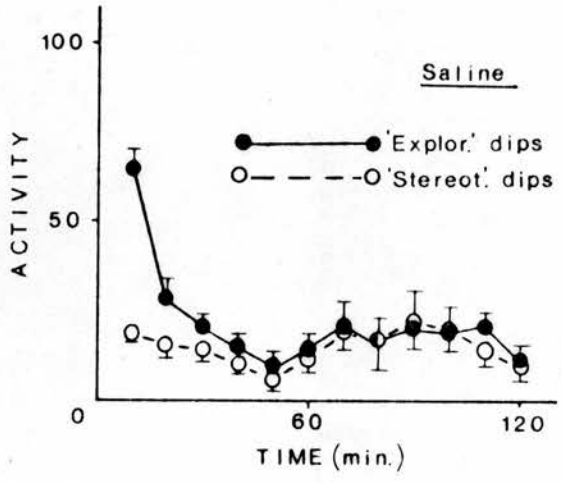


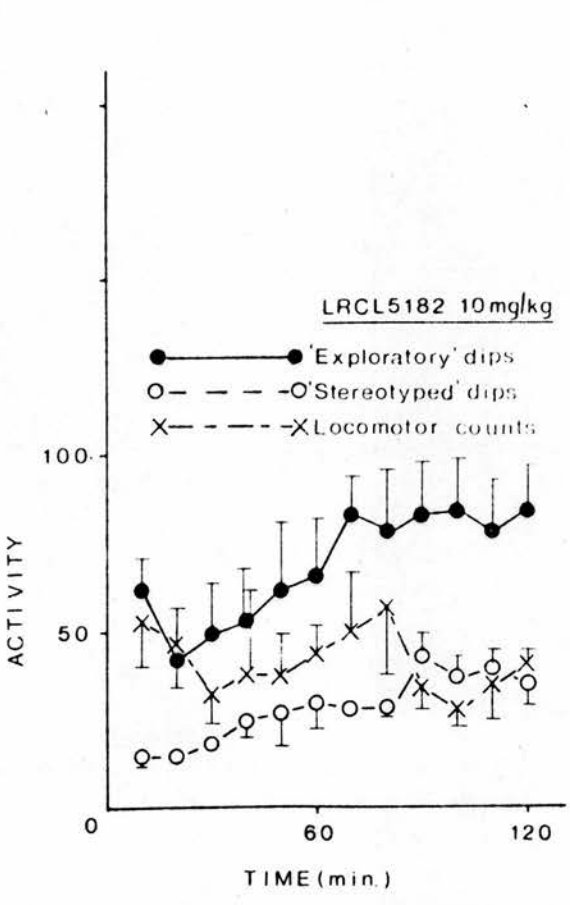
FIG. 31: Behavioural response in the hole-board apparatus following i.p. administration of 1 ml/kg saline and effect of pretreatment with desmethylimipramine hydrochloride 25 mg/kg (DMI), chlorimipramine hydrochloride 25 mg/kg (CMI) or GEA 654 50 mg/kg (a neuronal 5-HT uptake inhibitor) 30 min. before on response to administration of 1 ml/kg saline. Each point represents mean activity ± S.E.M. during successive 10 min. intervals after the saline injection.

GEA 654 (Fig.31d,Tables 15,16) caused a slight increase in "exploratory" dipping and locomotor counts which however were not statistically significant. Animals given this drug appeared more aroused and more excitable than control animals.

LRCL 5182 produced a marked, dose-related increase in activity on the hole-board. At the lower dose (10 mg/kg) dipping behaviour was greatly increased, this being of predominantly "exploratory" type (Fig.32,Tables 17,18) with a correspondingly low S/T ratio. At the higher dose (20 mg/kg) dipping behaviour further increased, but this time"stereotyped" dipping was more prominent and the S/T ratio was higher (Fig.32,Tables 17,18)."Non-dipping stereotyped behaviour" defined as repetitive head movements, including side-to-side as well as up and down movements and also involving gnawing and biting at the hole-edges (see page 146) was commonly seen with the highest dose of LRCL 5182 during the second hour of the recording.

Locomotor activity was also markedly stimulated and this was more marked at a dose of 20 mg/kg. This seemed, at first, surprising since intense stereotyped dipping is usually associated with a reduction in locomotor activity. However, locomotor activity stimulation was confirmed visually; animals were observed to divide their time between rushing around the hole-board, and dipping repeatedly into holes. Even intense "non-dipping stereotyped behaviour" in some animals was observed to persist even during marked locomotor stimulation. There is a large variance in activity levels recorded at the higher





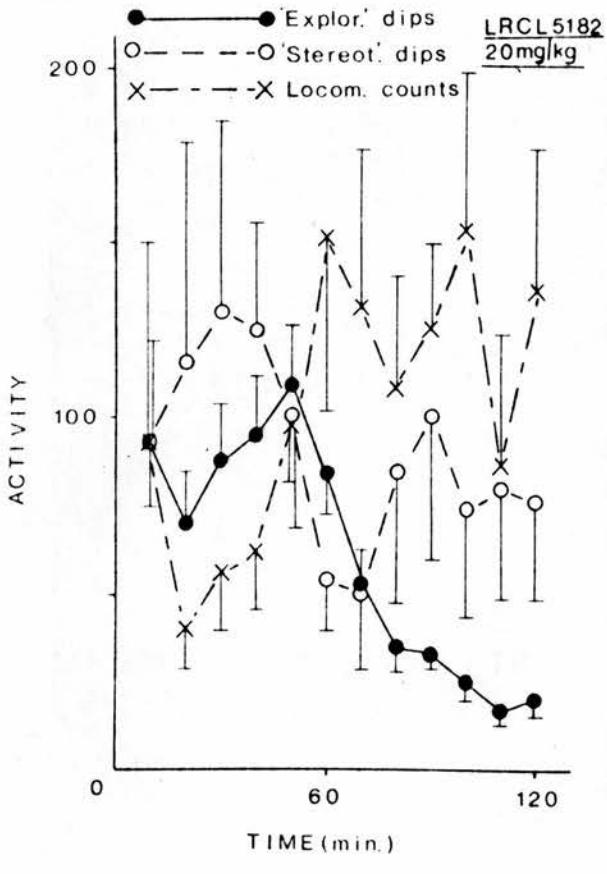


FIG. 32a: Behavioural response in the hole-board apparatus following i.p. administration of 1 ml/kg saline or 10 or 20 mg/kg LRCL 5182 (a neuronal dopamine uptake inhibitor). Each point represents mean activity ± S.E.M. of 5 or 6 rats during successive 10 min. intervals following the injection.

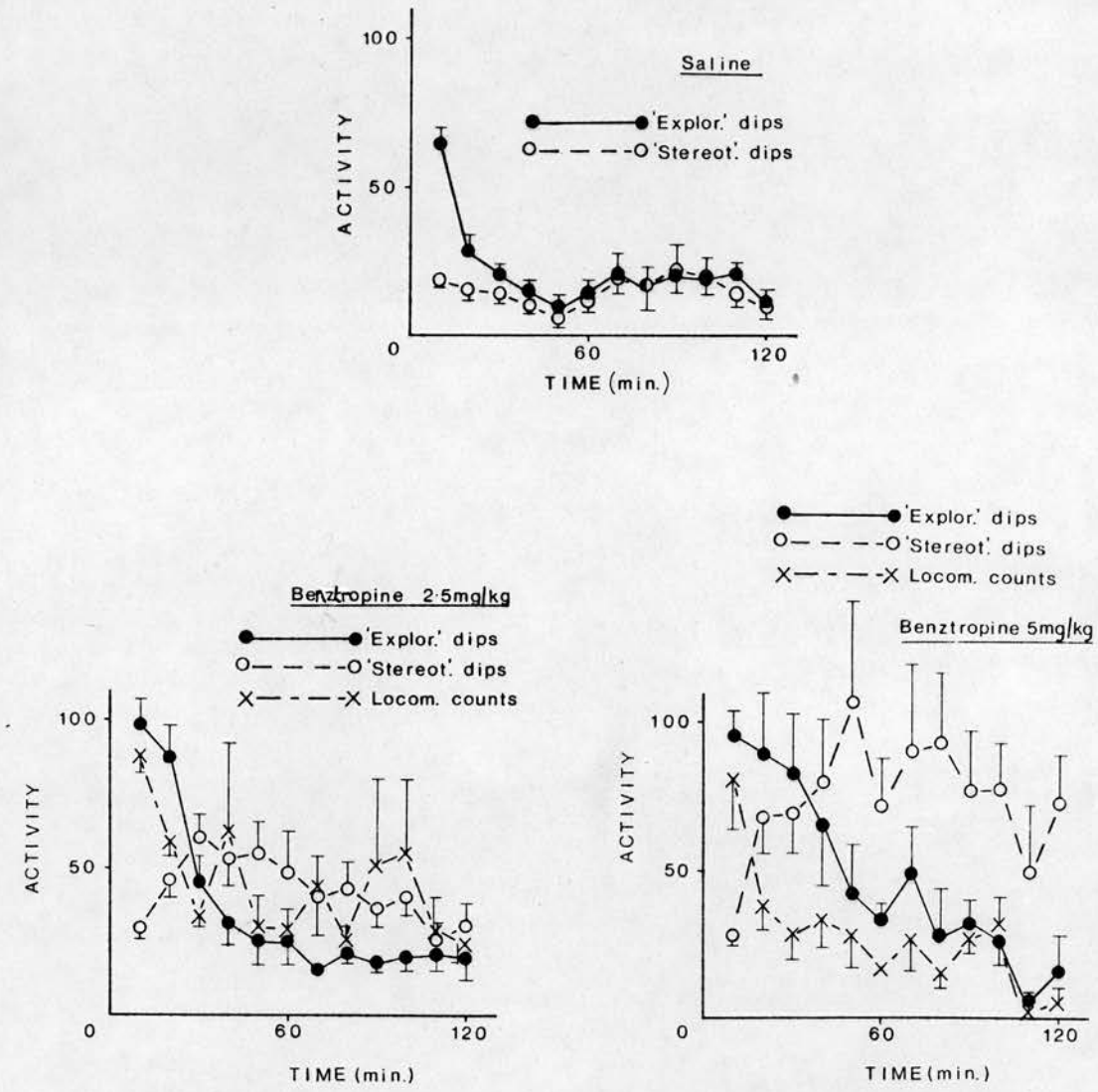


FIG. 32b: Behavioural response in the hole-board apparatus following i.p. administration of 1 ml/kg saline or 2.5 or 5.0 mg/kg benztropine (a neuronal dopamine uptake inhibitor). Each point represents mean activity ± S.E.M. of 6 rats during successive 10 min. intervals following the injection.

TABLE 17: Behaviour of rats in the hole-board apparatus following administration of 1 ml/kg saline or 10 or 20 mg/kg "LRCL 5182" or 2.5 or 5.0 mg/kg benztropine mesylate i.p. Figures denote mean activity ± S.E.M. during successive 10 min. intervals after injection. Five or 6 animals were studied at each dose level.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts.

Details of the responses of individual rats, can be found in the Appendix (Tables, 1,16-19)

TIME INTERVAL (min)	0 - 10			10 - 20		
TREATMENT	S	E	LOC	S	E	LOC
0	18 ± 2	64 ± 5	48 ± 5	16 ± 4	28 ± 7	31 ± 7
LRCL 5182 10 mg/kg	14 ± 4	62 ± 10	53 ± 14	14 ± 1	42 ± 9	47 ± 11
LRCL 5182 20 mg/kg	93 ± 63	93 ± 20	93 ± 32	116 ± 71	70 ± 17	40 ± 12
Benztropine 2.5 mg/kg	29 ± 5	98 ± 10	88 ± 7	46 ± 8	87 ± 12	59 ± 5
Benztropine 5.0 mg/kg	28 ± 4	96 ± 10	81 ± 19	68 ± 14	89 ± 23	38 ± 9
TIME INTERVAL (min)	20 - 30			30 - 40		
TREATMENT	S	E	LOC	S	E	LOC
0	14 ± 4	21 ± 4	30 ± 7	10 ± 3	15 ± 4	18 ± 7
LRCL 5182 10 mg/kg	18 ± 2	49 ± 17	32 ± 9	24 ± 7	53 ± 18	53 ± 28
LRCL 5182 20 mg/kg	130 ± 61	88 ± 18	57 ± 19	125 ± 34	95 ± 18	62 ± 19
Benztropine 2.5 mg/kg	60 ± 8	45 ± 10	34 ± 4	53 ± 11	31 ± 7	62 ± 35
Benztropine 5.0 mg/kg	69 ± 16	83 ± 22	29 ± 9	80 ± 24	65 ± 23	33 ± 10
TIME INTERVAL (min)	40 - 50			50 - 60		
TREATMENT	S	E	LOC	S	E	LOC
0	6 ± 3	10 ± 4	9 ± 4	12 ± 4	13 ± 4	14 ± 5
LRCL 5182 10 mg/kg	27 ± 11	62 ± 22	38 ± 13	29 ± 8	66 ± 18	44 ± 9
LRCL 5182 20 mg/kg	101 ± 17	109 ± 19	99 ± 35	54 ± 17	84 ± 14	152 ± 56
Benztropine 2.5 mg/kg	54 ± 12	25 ± 9	30 ± 12	48 ± 17	25 ± 9	29 ± 8
Benztropine 5.0 mg/kg	107 ± 38	42 ± 19	28 ± 12	72 ± 18	33 ± 7	17 ± 1

(Contd.)

TABLE 17: continued

TIME INTERVAL (min)	60 - 70			70 - 80		
TREATMENT	S	E	LOC	S	E	LOC
0	19 ± 5	21 ± 8	19 ± 5	17 ± 10	17 ± 5	12 ± 4
LRCL 5182 10 mg/kg	28 ± 2	83 ± 19	50 ± 12	28 ± 3	78 ± 20	57 ± 22
LRCL 5182 20 mg/kg	50 ± 24	53 ± 10	132 ± 50	85 ± 42	36 ± 8	109 ± 34
Benztropine 2.5 mg/kg	40 ± 14	15 ± 2	43 ± 11	43 ± 11	21 ± 3	25 ± 4
Benztropine 5.0 mg/kg	90 ± 28	49 ± 18	26 ± 10	93 ± 27	28 ± 11	15 ± 5
TIME INTERVAL (min)	80 - 90			90 - 100		
TREATMENT	S	E	LOC	S	E	LOC
0	22 ± 8	20 ± 7	16 ± 4	20 ± 5	18 ± 5	17 ± 4
LRCL 5182 10 mg/kg	43 ± 8	83 ± 18	34 ± 7	37 ± 7	84 ± 17	28 ± 5
LRCL 5182 20 mg/kg	101 ± 44	33 ± 5	126 ± 25	74 ± 34	25 ± 5	154 ± 51
Benztropine 2.5 mg/kg	36 ± 8	18 ± 4	51 ± 32	40 ± 6	19 ± 4	55 ± 27
Benztropine 5.0 mg/kg	77 ± 22	32 ± 9	27 ± 5	77 ± 17	26 ± 9	32 ± 10
TIME INTERVAL (min)	100 - 110			110 - 120		
TREATMENT	S	E	LOC	S	E	LOC
0	14 ± 4	21 ± 5	18 ± 5	10 ± 4	12 ± 4	17 ± 7
LRCL 5182 10 mg/kg	39 ± 7	78 ± 15	35 ± 11	35 ± 7	84 ± 14	41 ± 4
LRCL 5182 20 mg/kg	81 ± 35	17 ± 5	87 ± 38	77 ± 29	20 ± 5	137 ± 44
Benztropine 2.5 mg/kg	26 ± 9	21 ± 6	27 ± 12	30 ± 9	19 ± 8	24 ± 7
Benztropine 5.0 mg/kg	49 ± 25	6 ± 3	2 ± 1	73 ± 18	38 ± 13	16 ± 5

TABLE 18: Overall behavioural response in the hole-board apparatus during a 2 hour period following i.p. administration of 1 ml/kg saline or 10 or 20 mg/kg "LRCL 5182" or 2.5 or 5.0 mg/kg benztropine mesylate. Figures show the response of each of a group of 5 or 6 rats under any one treatment. A total of 20 animals were employed.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

DOSE (mg/kg)	ACTIVITY	RAT NO.						MEAN ± SEM
		1	2	3	4	5	6	
Saline 1 ml/kg	S	132	107	239	246	211	141	179 ± 24
	E	265	191	274	350	307	178	261 ± 26
	T	397	298	513	596	518	319	440 ± 49
	S/T	0.33	0.36	0.47	0.41	0.41	0.44	0.40 ± 0.02
	LOC	287	150	211	386	187	284	251 ± 35
LRCL 5182 10 mg/kg	S	185	352	420	324	404		337 ± 41
	E	329	1180	860	464	1292		825 ± 190
	T	514	1532	1280	788	1696		1162 ± 223
	S/T	0.36	0.23	0.33	0.41	0.24		0.31 ± 0.03
	LOC	298	879	648	293	417		507 ± 113
LRCL 5182 20 mg/kg	S	431	914	1786	1828	475	1105	1090 ± 248
	E	743	656	432	1017	647	864	726 ± 82
	T	1174	1570	2218	2845	1122	1969	1816 ± 271
	S/T	0.37	0.58	0.81	0.64	0.42	0.56	0.56 ± 0.07
	LOC	1670	937	1159	802	480	2448	1249 ± 289
Benztropine 2.5 mg/kg	S	517	195	452	606	342	918	504 ± 101
	E	653	263	476	463	233	468	426 ± 64
	T	1170	458	928	1069	575	1386	931 ± 145
	S/T	0.44	0.43	0.49	0.57	0.59	0.66	0.53 ± 0.03
	LOC	636	630	-	459	-	670	599 ± 47
Benztropine 5.0 mg/kg	S	809	794	103	1778	479	1348	885 ± 245
	E	962	592	296	344	1054	279	588 ± 141
	T	1771	1386	399	2122	1533	1627	1473 ± 238
	S/T	0.46	0.57	0.26	0.84	0.31	0.83	0.54 ± 0.10
	LOC	415	300	201	155	586	-	331 ± 76

Kruskal-Wallis one-way analysis of variance. For the behavioural responses with the two doses of LRCL 5182 and saline: $p < 0.01$ for "stereotyped" dips, "exploratory" dips, S/T ratio and locomotor counts. For the behavioural changes with the two doses of benztropine and saline: $p < 0.05$ for "stereotyped" dips < 0.02 for locomotor counts.

dose, particularly in locomotor counts. This variation in the locomotor response was confirmed visually.

A Kruskal-Wallis one-way analysis of variance showed that the differences in overall response between saline-treated controls and animals treated with 10 and 20 mg/kg LRCL 5182 were statistically significant ($p < 0.01$ for "stereotyped" dips, "exploratory" dips, locomotor counts and the S/T ratio).

Benztropine mesylate produced a dose-dependent increase in behaviour on the hole-board. At 2.5 mg/kg both "exploratory" and "stereotyped" dipping were stimulated as was locomotor activity (Fig.32, Tables 17,18). At 5.0 mg/kg the further increase in dipping behaviour involved both "stereotyped" and "exploratory" types while locomotor activity was less affected in comparison with the lower dose.

A Kruskal-Wallis one-way analysis of variance comparing the effects of the two doses of benztropine with saline-treated controls showed that the differences were statistically significant ($p < 0.05$ for "stereotyped" dips and < 0.02 for locomotor counts). The differences in "exploratory" dips and S/T ratio were not significant.

Fig.33 summarizes the results for all the monoamine uptake inhibitors studied.

(b) Effects of pretreatment with desmethylimipramine hydrochloride (DMI), chlorimipramine hydrochloride (CMI), GEA 654 and 'SKF-525A' on the response to 4 mg/kg DL-amphetamine sulphate

DMI (25 mg/kg), CMI (25 mg/kg) and GEA 654 (50 mg/kg) i.p. were administered i.p. 30 min. before amphetamine injection

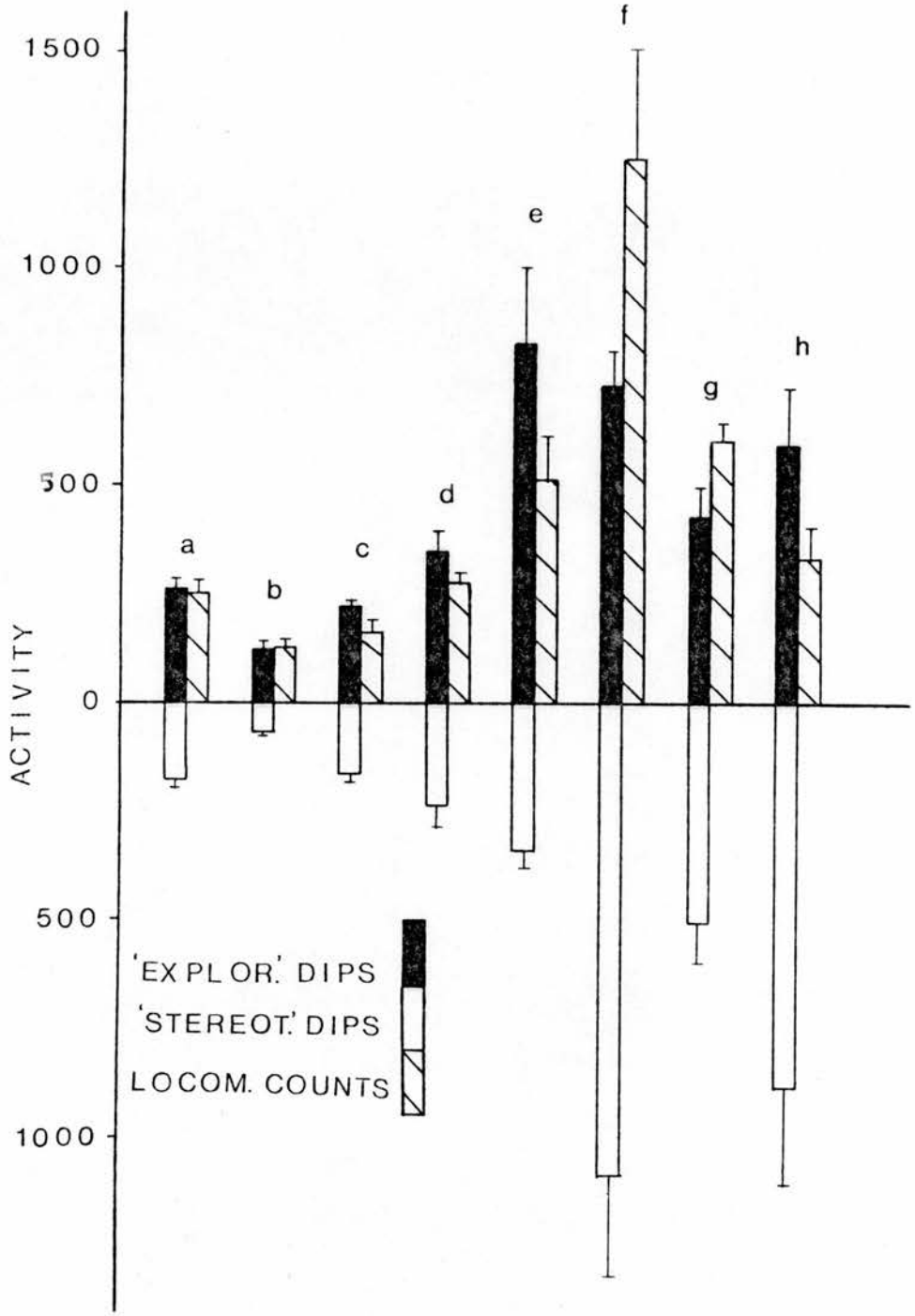


FIG. 33: Overall activity in the hole-board apparatus during a 2 hour period following i.p. administration of (a) 1 ml/kg saline, (b) 25 mg/kg desmethylimipramine hydrochloride 30 min. before 1 ml/kg saline, (c) 25 mg/kg chlorimipramine hydrochloride 30 min. before 1 ml/kg saline, (d) 50 mg/kg GEA 654 30 min. before 1 ml/kg saline, (e) 10 mg/kg LRCL 5182, (f) 20 mg/kg LRCL 5182, (g) 2.5 mg/kg benztropine mesylate or (h) 5.0 mg/kg benztropine mesylate. Each column represents mean ± S.E.M. of 5 or 6 ratsduring the entire two hour period following the final or only injection.

while SKF-525A (15 or 30 mg/kg, Fig.30) was administered 40 minutes before the amphetamine. The responses were compared to those of rats treated with 4 mg/kg DL-amphetamine sulphate only.

The results are presented in Fig.34 and Tables 19 and 20 and summarized in Fig. 35.

All four drugs had similar effects on the amphetamine response which was markedly potentiated. The initial burst of exploratory dipping and locomotor activity was not much affected except in the case of DMI, where this exploratory burst was diminished (Fig.34b) ($p = 0.064$ i.e. not significant for "exploratory" dips, $p = 0.030$ for locomotor counts). This was probably a result of the "sedative" effects observed when the drug was given before saline (Fig. 31b). The level of hole-dipping thereafter markedly increased in all four groups of animals and the pattern became markedly "stereotyped" with an associated decrease from the initial level in locomotor counts. The intensity and pattern of hole-dipping seen with the uptake inhibitors as well as at the higher dose of SKF-525A (30 mg/kg) approached that seen after double the dose of amphetamine (i.e 8 mg/kg) on its own (Fig.16).

Although DMI appeared to be the most effective of the drugs in depressing dipping activity when the drugs were given before saline, it also appeared to be the most potent in potentiating the behavioural response to amphetamine, since "non-dipping stereotyped behaviour" was observed in the majority of animals given the DMI - amphetamine combination but not in those given the other

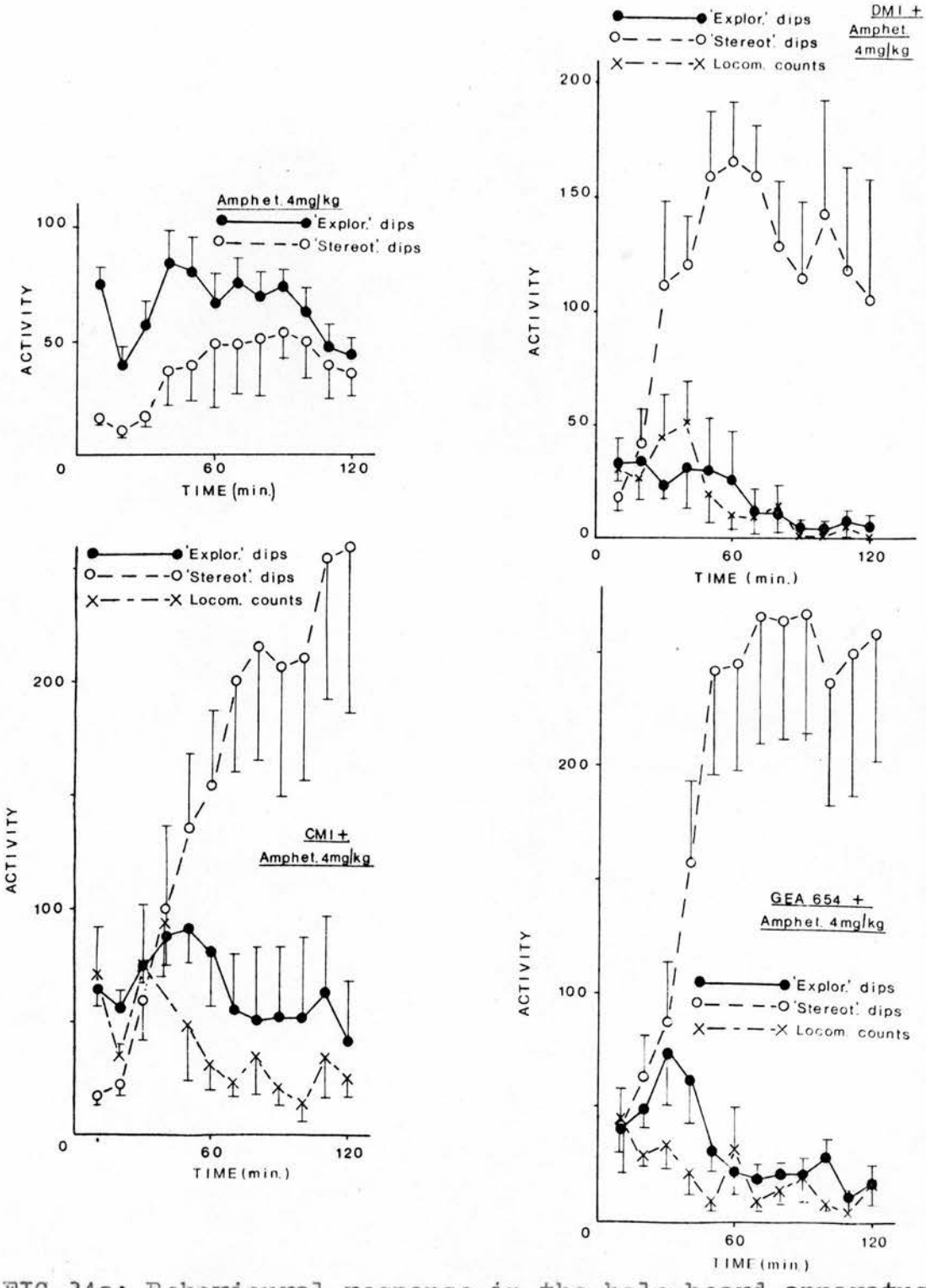


FIG. 34a: Behavioural response in the hole-board apparatus following i.p. administration of (a) 4 mg/kg DL-amphetamine sulphate and the effect on this response of pretreatment with (b) 25 mg/kg desmethylimipramine hydrochloride (DMI), (c) 25 mg/kg chlorimipramine hydrochloride (CMI) or (d) 50 mg/kg GEA 654 30 min. before the amphetamine injection. Each point represents mean activity ± S.E.M. of 6 rats during successive 10 min. intervals following the amphetamine injection.

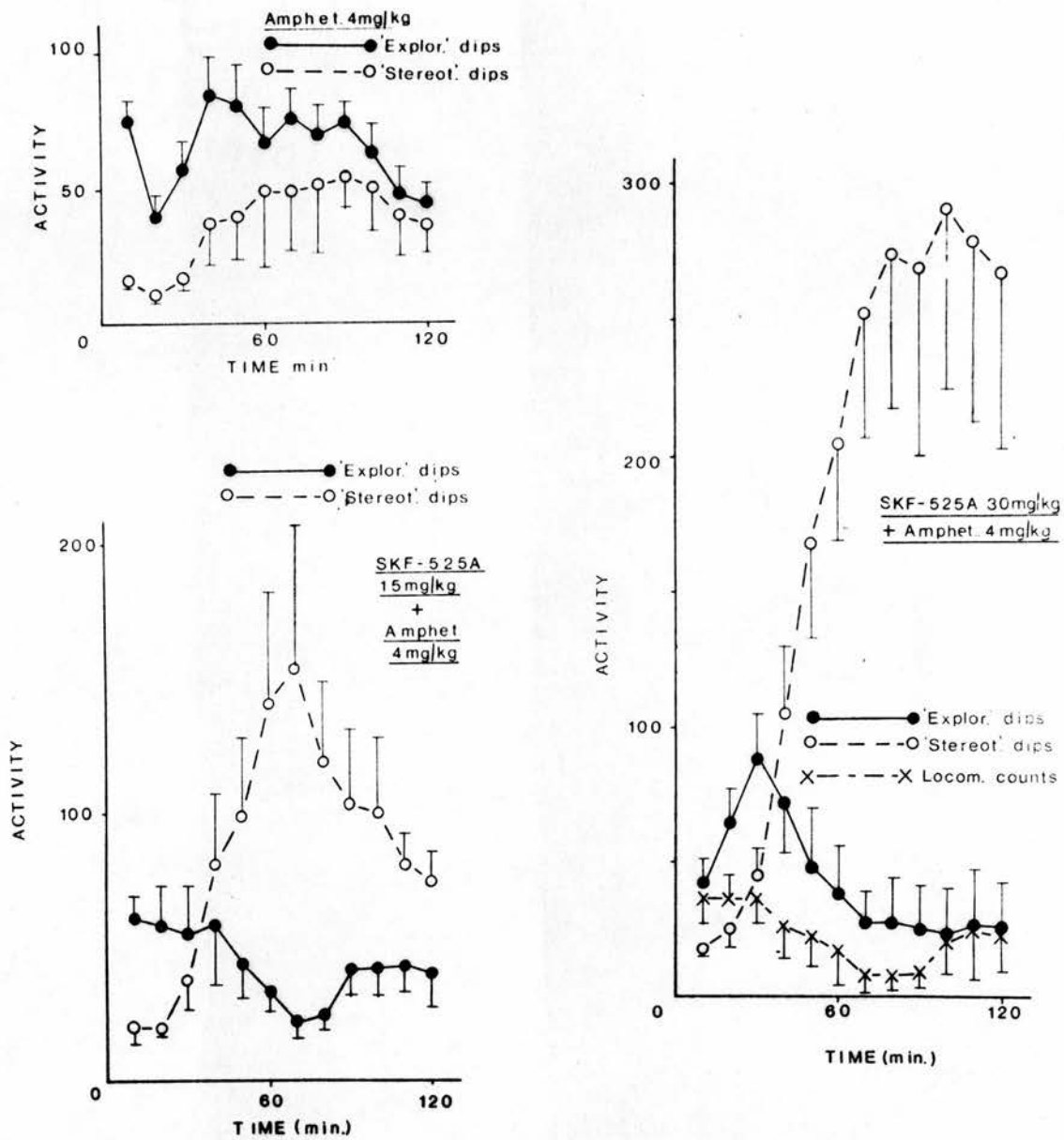


FIG. 34b: Behavioural response in the hole-board apparatus following i.p. administration of 4 mg/kg DL-amphetamine and effect on this response of pretreatment with 15 or 30 mg/kg SKF-525A (a hepatic microsomal enzyme inhibitor). Each point represents mean activity ± S.E.M. of 6 rats during successive 10 min. intervals following the amphetamine injection.

TABLE 19: Effects of pretreatment with desmethylimipramine HCL (DMI) 25 mg/kg, chlorimipramine HCL (CMI) 25 mg/kg, "GEA 654" 50 mg/kg 30 min. before or 15 or 30 mg/kg SKF-525A 40 min. before on the behavioural response to 4 mg/kg DL-amphetamine sulphate in the hole-board apparatus. Figures show mean response ± S.E.M. during successive 10 min. periods after amphetamine injection. Six animals were studied with each pretreatment.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts.

Details of the responses of individual rats can be found in the Appendix (Tables 3, 20-24).

TIME INTERVAL (min)	0 - 10			10 - 20		
PRETREATMENT	S	E	LOC	S	E	LOC
0	16 ± 3	75 ± 9	64 ± 8	11 ± 3	39 ± 8	36 ± 6
DMI 25 mg/kg	18 ± 6	33 ± 12	31 ± 9	42 ± 16	34 ± 10	26 ± 9
CMI 25 mg/kg	17 ± 5	64 ± 9	71 ± 23	22 ± 7	56 ± 9	35 ± 5
GEA 654 50 mg/kg	42 ± 24	40 ± 11	45 ± 14	63 ± 20	48 ± 9	29 ± 5
SKF-525A 15 mg/kg	20 ± 7	61 ± 9	42 ± 10	20 ± 3	58 ± 17	45 ± 22
SKF-525A 30 mg/kg	17 ± 3	42 ± 10	36 ± 11	25 ± 7	64 ± 13	36 ± 10
TIME INTERVAL (min)	20 - 30			30 - 40		
PRETREATMENT	S	E	LOC	S	E	LOC
0	17 ± 4	57 ± 11	62 ± 10	37 ± 17	84 ± 15	52 ± 9
DMI 25 mg/kg	112 ± 39	23 ± 6	44 ± 21	121 ± 23	31 ± 20	51 ± 19
CMI 25 mg/kg	59 ± 19	75 ± 9	75 ± 30	99 ± 31	87 ± 14	93 ± 28
GEA 654 50 mg/kg	87 ± 29	74 ± 25	33 ± 12	157 ± 39	62 ± 20	21 ± 10
SKF-525A 15 mg/kg	38 ± 12	55 ± 19	41 ± 22	81 ± 28	58 ± 24	35 ± 20
SKF-525A 30 mg/kg	45 ± 11	88 ± 18	36 ± 9	105 ± 28	72 ± 20	26 ± 13

(Contd.)

TABLE 19: continued

TIME INTERVAL (min)	40 - 50			50 - 60		
PRETREATMENT	S	E	LOC	S	E	LOC
0	39 ± 17	81 ± 18	44 ± 12	48 ± 31	67 ± 14	53 ± 6
DMI 25 mg/kg	159 ± 32	30 ± 26	19 ± 17	166 ± 28	26 ± 23	10 ± 6
CMI 25 mg/kg	135 ± 37	91 ± 15	48 ± 27	154 ± 37	81 ± 26	31 ± 12
GEA 654 50 mg/kg	242 ± 51	31 ± 10	9 ± 4	245 ± 51	22 ± 10	32 ± 20
SKF-525A 15 mg/kg	98 ± 34	44 ± 14	43 ± 16	140 ± 46	33 ± 8	37 ± 21
SKF-525A 30 mg/kg	168 ± 39	48 ± 24	22 ± 13	204 ± 39	38 ± 10	17 ± 14
TIME INTERVAL (min)	60 - 70			70 - 80		
PRETREATMENT	S	E	LOC	S	E	LOC
0	49 ± 24	76 ± 12	51 ± 5	51 ± 27	70 ± 12	57 ± 7
DMI 25 mg/kg	159 ± 25	12 ± 12	9 ± 8	128 ± 32	10 ± 9	13 ± 12
CMI 25 mg/kg	201 ± 44	56 ± 27	23 ± 7	215 ± 57	51 ± 35	35 ± 19
GEA 654 50 mg/kg	266 ± 62	18 ± 6	9 ± 5	264 ± 57	21 ± 8	13 ± 7
SKF-525A 15 mg/kg	153 ± 56	22 ± 7	25 ± 6	118 ± 34	24 ± 5	19 ± 7
SKF-525A 30 mg/kg	252 ± 50	27 ± 13	8 ± 8	273 ± 62	27 ± 19	8 ± 7
TIME INTERVAL (min)	80 - 90			90 - 100		
PRETREATMENT	S	E	LOC	S	E	LOC
0	53 ± 18	74 ± 9	55 ± 8	50 ± 18	63 ± 12	51 ± 17
DMI 25 mg/kg	114 ± 37	4 ± 4	1 ± 1	143 ± 54	3 ± 3	0 ± 0
CMI 25 mg/kg	206 ± 64	52 ± 35	21 ± 9	210 ± 59	52 ± 38	14 ± 9
GEA 654 50 mg/kg	267 ± 58	21 ± 8	20 ± 11	237 ± 60	28 ± 10	8 ± 3
SKF-525A 15 mg/kg	103 ± 30	41 ± 10	22 ± 7	100 ± 31	41 ± 11	21 ± 6
SKF-525A 30 mg/kg	268 ± 75	24 ± 19	9 ± 6	289 ± 72	23 ± 19	20 ± 14

(Contd.)

TABLE 19: continued

TIME INTERVAL (min)	100 - 110			110 - 120		
PRETREATMENT	S	E	LOC	S	E	LOC
0	39 ± 16	47 ± 11	48 ± 17	36 ± 11	44 ± 9	51 ± 21
DMI 25 mg/kg	117 ± 51	7 ± 6	0.3 ± 0.3	105 ± 58	5 ± 5	0.3 ± 0.3
CMI 25 mg/kg	254 ± 69	46 ± 38	34 ± 19	259 ± 80	41 ± 30	25 ± 9
GEA 654 50 mg/kg	250 ± 69	11 ± 4	3 ± 2	258 ± 60	17 ± 8	17 ± 11
SKF-525A 15 mg/kg	80 ± 13	42 ± 10	28 ± 13	74 ± 12	39 ± 13	22 ± 9
SKF-525A 30 mg/kg	278 ± 73	26 ± 23	25 ± 21	266 ± 70	25 ± 19	23 ± 15

TABLE 20: Effects of pretreatment with Desmethylimipramine HCL (DMI) 25 mg/kg, Chlorimipramine HCL (CMI) 25 mg/kg, "GEA 654" 50 mg/kg 30 min. before or 15 or 30 mg/kg "SKF-525A" 40 min. before on the overall behavioural response in the hole-board apparatus to 4 mg/kg DL-amphetamine sulphate during a two hour period. Figures show the response of each of a group of six rats under any one treatment.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

TREATMENT	ACT-IVITY	RAT NO. 1	2	3	4	5	6	MEAN ± SEM
Amphetamine 4 mg/kg	S	163	242	1306	366	228	374	446 ± 175
	E	862	771	518	566	862	1098	779 ± 88
	T	1025	1013	1824	932	1090	1472	1226 ± 142
	S/T	0.16	0.24	0.72	0.39	0.21	0.25	0.33 ± 0.08
	LOC	894	509	759	497	-	467	625 ± 83
DMI 25 mg/kg + Amphetamine 4 mg/kg	S	1953	773	1714	988	824	2034	*1381 ± 238
	E	304	76	23	139	86	685	**219 ± 101
	T	2257	849	1737	1127	910	2719	1600 ± 314
	S/T	0.87	0.91	0.99	0.88	0.91	0.75	****0.88 ± 0.03
	LOC	180	380	23	106	150	-	**168 ± 58
CMI 25 mg/kg + Amphetamine 4 mg/kg	S	3231	416	1677	2109	1231	2319	**1830 ± 394
	E	523	2063	455	394	727	361	754 ± 267
	T	3754	2479	2132	2503	1958	2686	2585 ± 257
	S/T	0.86	0.17	0.79	0.84	0.63	0.86	0.69 ± 0.11
	LOC	214	967	368	268	431	357	434 ± 110
GEA 654 50 mg/kg + Amphetamine 4 mg/kg	S	3036	1393	4606	2182	1180	1871	***2378 ± 520
	E	146	473	616	412	489	226	**394 ± 72
	T	3182	1866	5222	2594	1669	2097	2771 ± 539
	S/T	0.95	0.75	0.88	0.84	0.71	0.89	***0.84 ± 0.04
	LOC	88	69	346	251	359	92	***200 ± 55

Mann-Whitney U-test - Comparison of results with those given amphetamine alone.

**** p = 0.002
*** p = 0.004
** p = 0.008
* p = 0.016

(Contd.)

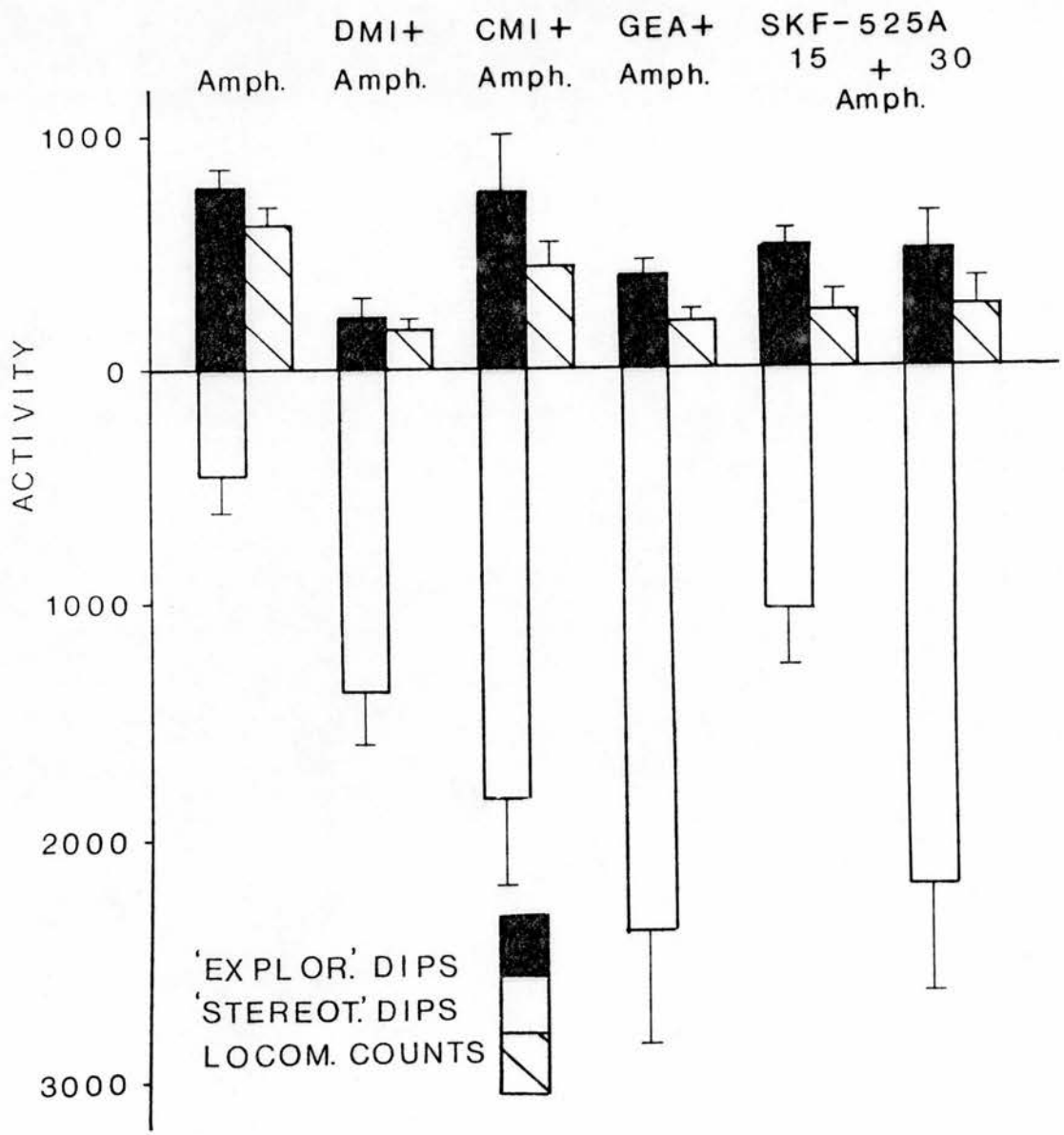


FIG. 35: Overall behavioural response during a 2 hour period following i.p. administration of 4 mg/kg DL-amphetamine sulphate (Amph.) and effect of pretreatment with 25 mg/kg desmethylimipramine hydrochloride (DMI), 25 mg/kg chlorimipramine hydrochloride (CMI), 50 mg/kg GEA 654 or 15 or 30 mg/kg SKF-525A on the response to 4 mg/kg DL-amphetamine sulphate (Amph.). Each column represents mean activity ± S.E.M. of 6 rats during the entire two hour period immediately following the amphetamine injection.

TABLE 20: continued

TREATMENT	ACT-IVITY	RAT NO. 1	2	3	4	5	6	MEAN ± SEM
SKF-525A 15 mg/kg + Amphetamine 4 mg/kg	S	953	399	284	1134	2025	1362	1026 ± 263
	E	312	729	409	730	379	551	518 ± 74
	T	1265	1128	693	1864	2404	1913	1544 ± 255
	S/T	0.75	0.35	0.41	0.61	0.84	0.71	0.61 ± 0.08
	LOC	228	227	217	279	-	737	238 ± 100
SKF-525A 30 mg/kg + Amphetamine 4 mg/kg	S	3573	2799	1198	473	2039	3054	2189 ± 483
	E	288	79	520	1304	464	364	503 ± 172
	T	3861	2878	1718	1777	2503	3418	2692 ± 354
	S/T	0.93	0.97	0.70	0.27	0.81	0.89	0.76 ± 0.11
	LOC	114	26	174	875	292	90	262 ± 128

Kruskal-Wallis one-way analysis of variance: differences between behavioural responses with the two doses of SKF-525A and with no pretreatment ($p < 0.01$ for "stereotyped" dips, < 0.02 S/T ratio).

drug-amphetamine combinations. Presumably it was this "non-dipping stereotyped behaviour" that was responsible for the decrease in "stereotyped" dipping observed during the second hour compared with the first hour in the DMI-pretreated rats. The phenomenon has been described in more detail on page 146.

Consistent with the increase in 'stereotyped dipping' the locomotor stimulant effects of the amphetamine were reduced, as again would be expected with increasing amphetamine dosage.

The effects of SKF-525A on the amphetamine response were dose-related, the higher dose producing a much more marked potentiation of the "stereotyped" dipping response to amphetamine.

A Mann-Whitney U-test showed that the effects of pre-treatment with DMI, CMI and GEA 654 on the overall response to 4 mg/kg DL-amphetamine sulphate, compared with the response to the same dose of amphetamine alone, were statistically significant at levels of 0.016, 0.008 and 0.004 respectively for "stereotyped" dips. For "exploratory" dips only the effects of DMI and GEA 654 were significant. ($p = 0.008$). For the S/T ratio the increases were significant for DMI and GEA 654 ($p = 0.002$ and 0.004 respectively) but not for CMI. For locomotor counts the differences with GEA 654 and DMI were significant ($p = 0.008$ and 0.004 respectively).

A Kruskal-Wallis one-way analysis of variance comparing the results with 15 and 30 mg/kg SKF-525A combined with amphetamine and with amphetamine alone showed that the differences were significant for "stereotyped" dips ($p < 0.01$)

and the S/T ratio ($p < 0.02$) but not significant for "exploratory" dips and locomotor counts.

(c) Plasma and Brain levels of amphetamine after intraperitoneal administration of DL-amphetamine sulphate and the effects of pretreatment with desmethylimipramine, chlorimipramine, 'GEA 654' and 'SKF-525A'

(i) Calibration curves

The calibration curve for plasma is shown in Fig. 36, the results being compared with those from solutions of DL-amphetamine sulphate in water. The limits of detection of amphetamine in plasma was in the region of 25 ng/ml. Peak heights for plasma extracts were virtually the same as those for water extracts. A linear relationship was demonstrated between peak height response on the gas chromatograph and the amounts of amphetamine in the samples between 25 and 500 ng. There was virtually no difference in peak height response between amphetamine standards in water and in plasma.

The standard curve for amphetamine added to whole brain tissue extracts in 0.4 M perchloric acid is shown in Fig. 37, again compared with those from amphetamine solutions in water. Again a linear relationship was demonstrated between peak height response and the amphetamine content of each sample between 250 ng and 5 µg. The results for different samples of plasma and brain were read off directly from standard curves produced on the day of each experiment.

(ii) Plasma and brain levels of amphetamine after systemic administration of DL-amphetamine sulphate

Rats in groups of five were injected intraperitoneally with 1 ml/kg saline or 4, 8 or 16 mg/kg DL-amphetamine sulphate. The animals were killed 60 minutes after the injection.

The results are presented in Fig. 38, Table 21. Brain levels of amphetamine were about 8 times those found in plasma. Amphetamine concentrations in plasma and brain increased with increasing dose of amphetamine but neither relationship was linear. Instead, increasing amphetamine doses appeared to cause disproportionately greater increases in plasma and tissue levels.

(iii) Effect of pretreatment with desmethylimipramine, chlorimipramine, GEA 654 and SKF-525A on plasma and brain levels of amphetamine after administration of 4 mg/kg DL-amphetamine sulphate i.p.

DMI (25 mg/kg), CMI (25 mg/kg) and GEA 654 (50 mg/kg) were administered i.p. 30 minutes before the amphetamine. SKF-525A (30 mg/kg) was administered 40 minutes before amphetamine. The animals were sacrificed 70 minutes after amphetamine injection. There were five animals in each group.

The estimates of brain and plasma amphetamine concentrations are shown in Fig. 39, Table 22. After all the pretreatments the concentrations of amphetamine in plasma and brain were markedly higher than those in saline-pretreated animals.

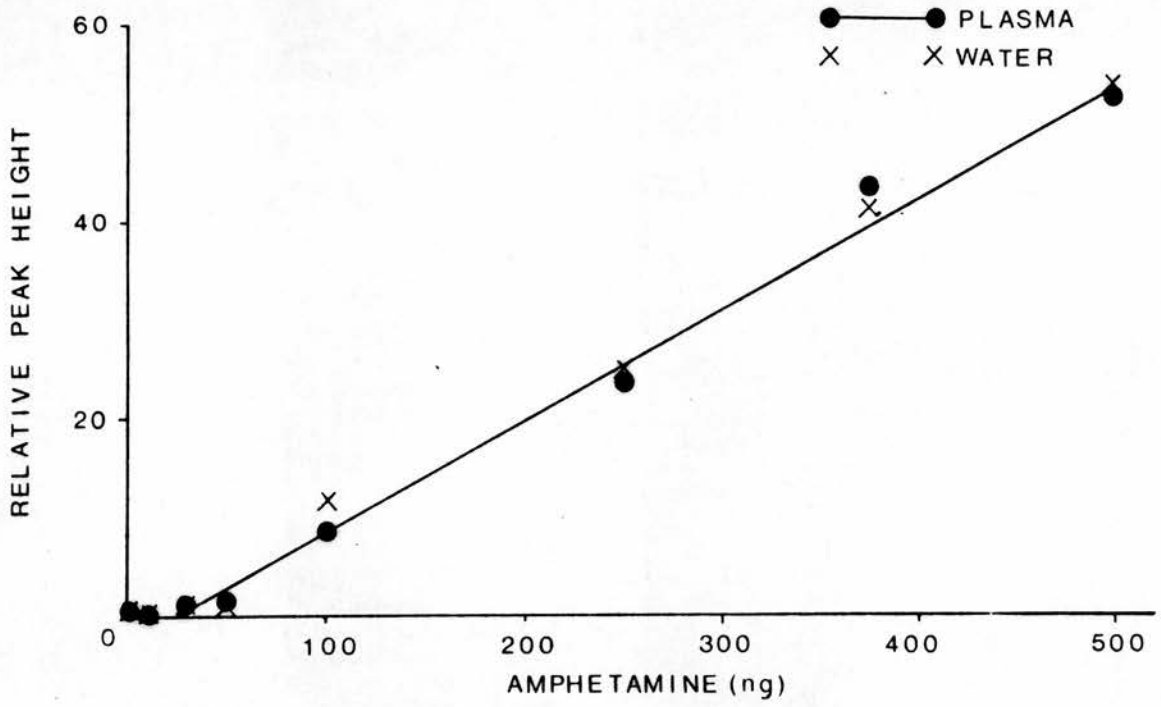


FIG. 36: A calibration curve for the assay of amphetamine in plasma by gas chromatography. The curve was determined following analysis of plasma from untreated rats to which the different amounts of amphetamine (as the DL-sulphate) were added - see page 126. Relative peak heights obtained from assay of amphetamine in distilled deionised water are also shown, although no curve is drawn for these.

At the dosages used, DMI appeared to be the most potent elevator of amphetamine levels (brain x 395%, plasma x 332%) followed by GEA 654 (325% and 256%). SKF-525A (320 and 225%) and chlorimipramine (224 and 216%). This rank order relates well to that of the respective treatments' abilities to potentiate the behavioural effects of amphetamine, in which respect 25 mg/kg DMI was the most and 25 mg/kg CMI the least effective.

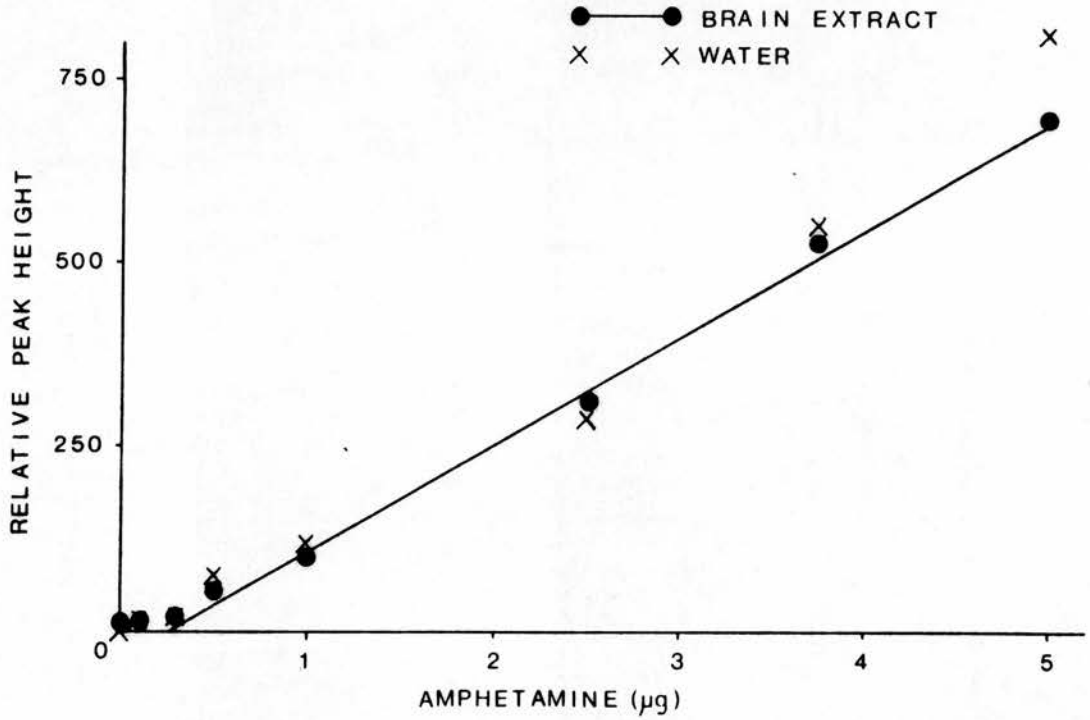


FIG. 37: A calibration curve for the assay of amphetamine in brain tissue extracts in 0.4 M perchloric acid by gas chromatography. The curve was determined following analysis of brain extract from untreated rats to which the different amounts of amphetamine (as the DL-sulphate) were added - see page 126. Relative peak heights obtained from assay of amphetamine in distilled deionised water are also shown, although no curve is drawn for these.

TABLE 21: Plasma and brain concentrations of amphetamine 60 min. after i.p. injection of 1 ml/kg saline or 4, 8 or 16 mg/kg DL-amphetamine sulphate into rats. Five animals were treated with each dose.

AMPHETAMINE DOSE (mg/kg)	RAT NO.	PLASMA CONCENTRATIONS (ng/ml)	BRAIN CONCENTRATIONS (µg/g)
0	1	< 25	< 0.25
	2	< 25	< 0.25
	3	< 25	< 0.25
	4	< 25	< 0.25
	5	< 25	< 0.25
	MEAN ± SEM	< 25	< 0.25
4	1	94	0.95
	2	51	0.32
	3	85	0.85
	4	85	0.65
	5	77	0.35
	MEAN ± SEM	78 ± 7	0.62 ± 0.13
8	1	46	2.95
	2	215	2.00
	3	323	3.00
	4	461	2.60
	5	582	2.90
	MEAN ± SEM	325 ± 93	2.69 ± 0.19
16	1	1230	4.75
	2	2815	10.75
	3	492	-
	4	1354	8.60
	5	1569	8.75
	MEAN ± SEM	1492 ± 377	8.21 ± 1.25

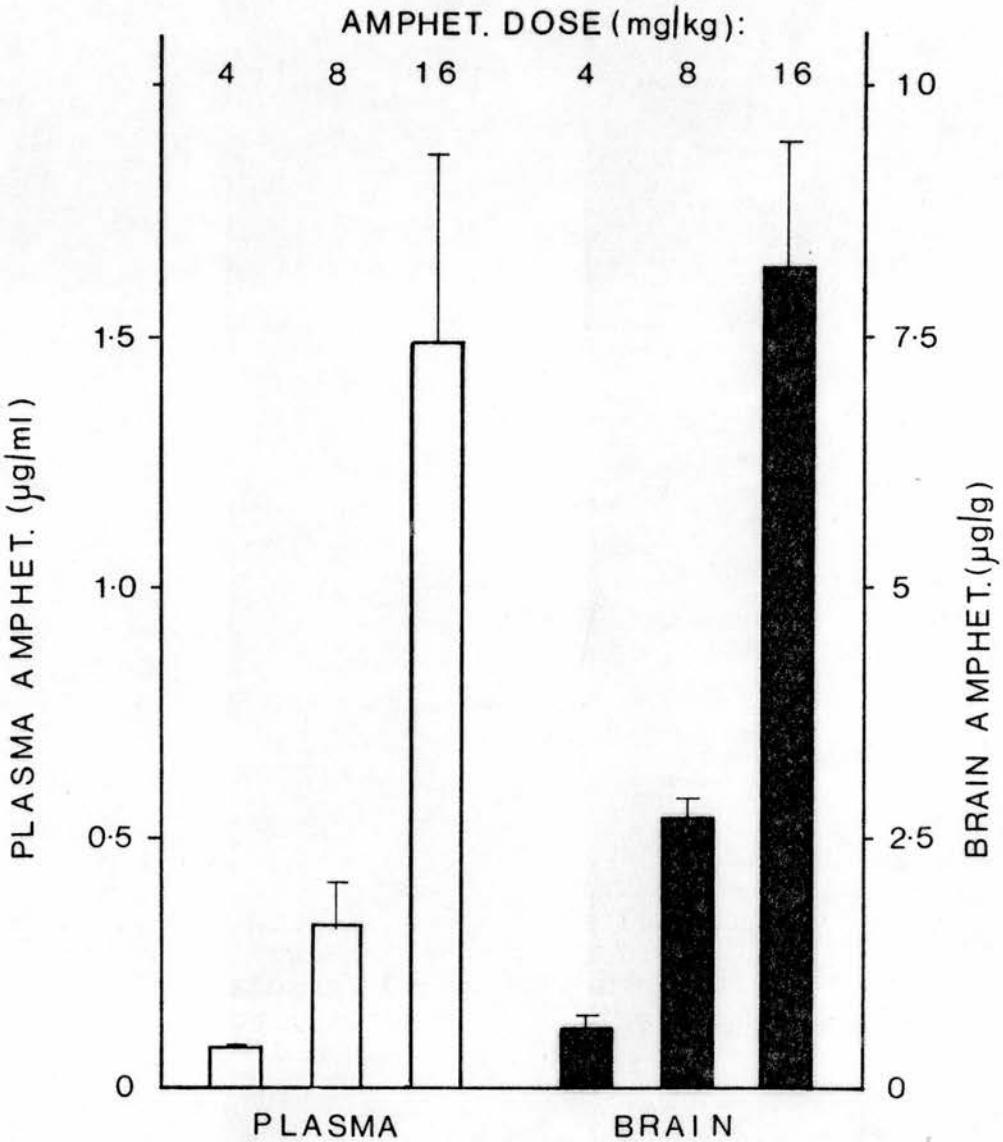


FIG. 38: Plasma and brain concentrations of amphetamine 60 min. after i.p. administration of 4, 8 or 16 mg/kg DL-amphetamine sulphate. Each column represents mean concentration ± S.E.M. from five animals.

TABLE 22: Effects on plasma and brain amphetamine levels of pretreatment with 1 ml/kg saline, 25 mg/kg Desmethylimipramine HCL (DMI), 25 mg/kg chlorimipramine HCL (CMI), 50 mg/kg "GEA 654" 30 min. before or 30 mg/kg "SKF-525A" 40 min. before administration of 4 mg/kg DL-amphetamine sulphate. Animals were killed 70 min. after the amphetamine injection.

TREATMENT	RAT NO.	PLASMA CONCENTRATIONS (µg/g)	BRAIN CONCENTRATIONS (µg/g)
Saline 1 ml/kg + Amphetamine 4 mg/kg	1	100	2.10
	2	115	1.58
	3	80	1.80
	4	100	2.55
	5	60	1.43
	MEAN ± SEM	91. ± 9	1.89 ± 0.20
DMI 25 mg/kg + Amphetamine 4 mg/kg	1	45	6.83
	2	340	-
	3	415	7.25
	4	460	7.50
	5	250	8.25
	MEAN ± SEM	*302 ± 73	***7.46 ± 0.30
CMI 25 mg/kg + Amphetamine 4 mg/kg	1	250	3.49
	2	265	4.50
	3	145	3.38
	4	130	5.40
	5	195	4.43
	MEAN ± SEM	**197 ± 27	***4.24 ± 0.37
"GEA 654" 50 mg/kg + Amphetamine 4 mg/kg	1	235	6.83
	2	115	2.51
	3	180	8.07
	4	315	6.75
	5	320	6.60
	MEAN ± SEM	**233 ± 39	**6.15 ± 0.95
"SKF-525A" 30 mg/kg + Amphetamine 4 mg/kg	1	110	5.51
	2	220	5.63
	3	230	4.84
	4	265	5.93
	5	200	8.40
	MEAN ± SEM	**205 ± 26	***6.06 ± 0.61

Student's "t" test (comparison of saline-pretreated rats with other pretreatments): * $p < 0.02$: ** $p < 0.01$: *** $p < 0.001$

For brain amphetamine concentrations: $p < 0.001$ for DMI vs CMI
$p < 0.05$ for CMI vs SKF-525A

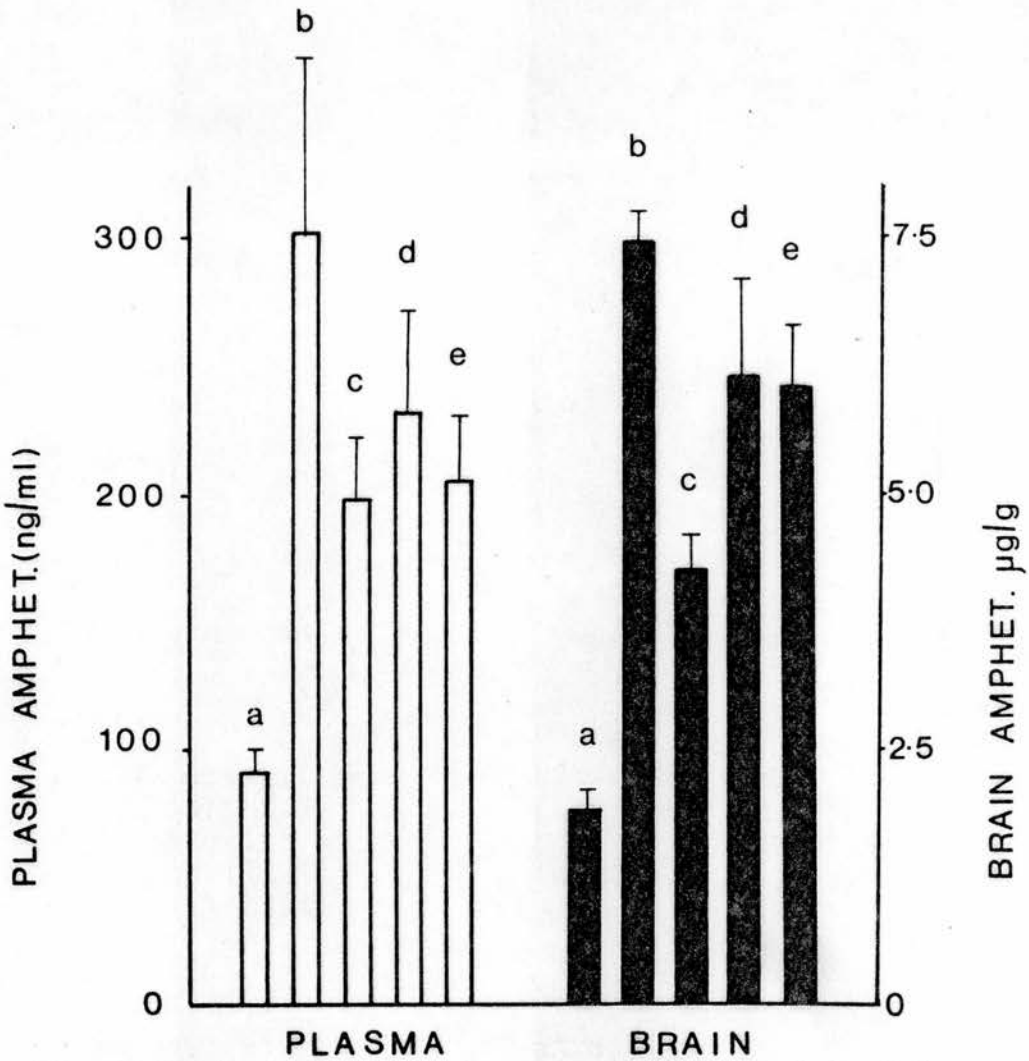


FIG. 39: Effect of i.p. pretreatment with (a) 1 ml/kg saline, (b) 25 mg/kg desmethylimipramine hydrochloride (DMI), (c) 25 mg/kg chlorimipramine hydrochloride (CMI), (d) 50 mg/kg GEA 654 30 min. before or 30 mg/kg SKF-525A 40 min. before administration of 4 mg/kg DL-amphetamine sulphate i.p. on plasma and brain amphetamine levels. Animals were killed 70 min. after the amphetamine injection. Each column represents mean amphetamine concentration ± S.E.M. for 5 rats.

B. STEREOTACTIC LESIONS OF ACCUMBENS AND CAUDATE NUCLEI

I. Effects of 6-hydroxydopamine-induced lesions of the accumbens and caudate nuclei

Ten to fourteen days after operation each animal was studied for one hour on the hole-board following administration of 1 ml/kg saline i.p. Seven days later the animal was again studied following 4 mg/kg DL-amphetamine sulphate and, after another seven days, 16 mg/kg DL-amphetamine sulphate. The illumination of the chamber was increased during the last study (i.e. after administration of 16 mg/kg amphetamine) so that "non-dipping stereotyped behaviour" could be more closely observed.

Preliminary analysis of the results of these experiments showed that consistent alteration in the pattern of behavioural changes to amphetamine were associated only with dopamine (DA) depletion of at least 65% in the accumbens nucleus or 75% in the caudate nucleus. Because of this, results are presented for those animals in which DA depletion to 35% or less was achieved in the accumbens nuclei and 25% or less in the striatum compared with sham-lesioned animals assayed in the same batch. These results are compared with those of the animals with sham lesions of the two nuclei, which are grouped together since there were no behavioural or biochemical differences between the two sham-lesioned groups. Results are also presented separately for those animals in which DA depletion did not reach the critical level for the production of behavioural changes (Tables 27,28).

(a) Biochemical analyses - Estimation of catecholamines in rat forebrain

Animals were killed and their brains removed for analysis of catecholamine distribution 21 days after the last behavioural testing. The delay was to minimize the effects of drug treatments on catecholamine levels.

(i) Standard calibration curves for dopamine and noradrenaline Different amounts of DA or NA were added to tissue extract prepared by homogenizing whole rat brain in 300 µl 0.1 N perchloric acid per 50 mg brain and carried through the procedure for assay of catecholamines. The final d.p.m. for samples of tissue extract containing no added catecholamine was subtracted from the d.p.m.s obtained from these standards so that a calibration curve could be obtained for the different amounts of DA or NA. Two estimates were made for each point on the curves. Results are presented in Figs. 40, 41 and Table 23. In both cases a linear relationship was obtained between the final d.p.m. and the DA or NA content of the standard put through the method. With the highest amounts of the monoamines, 150 and 200 ng, the d.p.m. values tended to fall off slightly. These two values were above the ranges of d.p.m. recorded in extracts from brain tissue samples assayed.

(ii) Control values Results obtained from sham-lesioned rats are presented in Figs. 42, 43 and Table 24.

TABLE 23: Calibration curve for Dopamine (DA) and Noradrenaline (NA) assay (see page 132).

Individual amounts of monoamine were added to 300 µl of rat brain tissue extract and assayed. The disintegrations per minute (D.P.M.) due to the added monoamine was estimated by subtracting the D.P.M. of the tissue extract samples from the total D.P.M. 'Tissue Blank' consisted of duplicate tubes put through the assay procedure with the O-methylation reaction inhibited by adding 0.5 M borate buffer before the incubation mixture and keeping it in an ice-bath (see page 73). Reagent blanks consisted of duplicate tubes of 300 µl 0.1M perchloric acid put through the procedure.

The tissue extract was prepared from rat brains in which the portion anterior to the anterior commissure had been removed. This explains the apparent discrepancy between the D.P.M.s of tissue extract blanks in the NA and DA fractions.

	DPM of DA fraction ($\times 10^{-3}$)		DPM of NA fraction ($\times 10^{-3}$)	
TUBE CONTENTS	TOTAL DPM	DPM Equivalent to added DA	TOTAL DPM	DPM Equivalent to added NA
Tissue Extract	5		23	
"	5		25	
12.5 ng DA	52	47	22	
"	52		22	
25 ng DA	105	99	22	
"	103		20	
50 ng DA	187	182	20	
"	188		20	
75 ng DA	217	214	18	
"	222		17	
100 ng DA	318	319	17	
"	330		15	
150 ng DA	422	403	16	
"	395		14	
200 ng DA	513	521	15	
"	545		13	
12.5 ng NA	6		37	16
"	6		40	
25 ng NA	8		60	35
"	8		58	

(Contd.)

TABLE 23: continued

TUBE CONTENTS	DPM of DA fraction ($x10^{-3}$)		DPM of NA fraction ($x10^{-3}$)	
	TOTAL DPM	DPM Equivalent to added DA	TOTAL DPM	DPM Equivalent to added NA
50 ng NA	10		98	73
"	10		96	
75 ng NA	11		111	87
"	11		112	
100 ng NA	15		162	138
"	15		162	
150 ng NA	17		198	180
"	20		211	
200 ng NA	19		245	225
"	22		253	
Tissue Blank	1.1		0.20	
"	1.2		0.29	
Reagent Blank	2.5		1.2	
"	2.9		1.1	

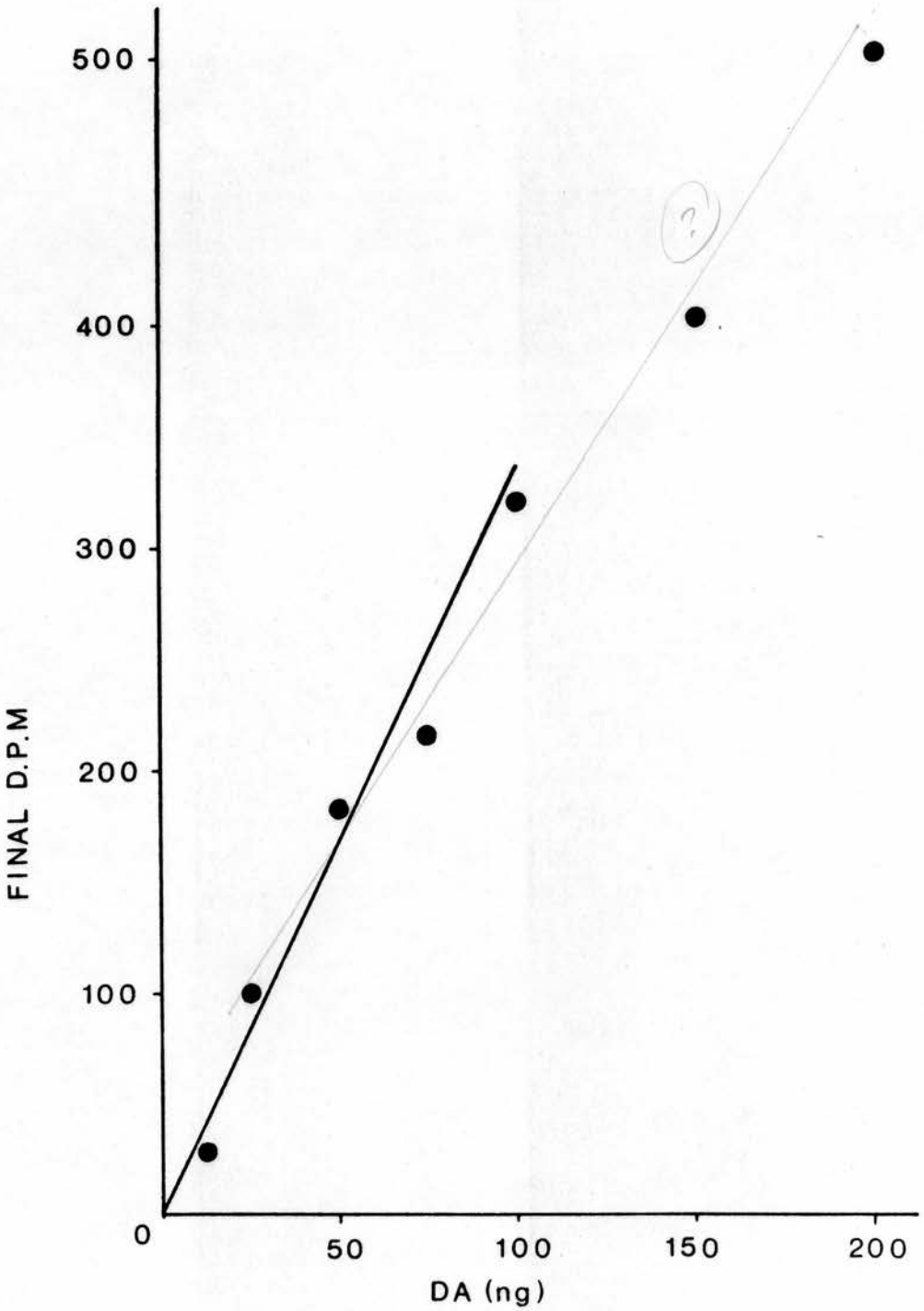


FIG. 40: Standard calibration curve for Dopamine (DA) assay. Each point represents mean disintegrations per minute (D.P.M.) x 10^{-3} obtained following assay in duplicate of different amounts of DA added to 300 µl brain tissue extract in 0.1 M perchloric acid (see page 132 and Table 23). The final DPM was obtained by subtracting the DPM produced by tissue extract samples from that of the sample.

TABLE 24: Overall behavioural responses in the hole-board apparatus of animals with "sham" lesions of the accumbens or caudate nuclei following administration of 1 ml/kg physiological saline, 4 mg/kg DL-amphetamine sulphate and 16 mg/kg DL-amphetamine sulphate in that order. The treatments were administered at weekly intervals.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.
Weight of the animals on the day of the first test is also shown.

At the bottom of the table are given the DA and NA contents of different brain areas.

TREATMENT	ACTIVITY	RAT NO.						
		1	2	3	4	5	6	7
Saline 1 ml/kg	S	165	170	80	98	135	148	
	E	311	159	122	213	348	222	
	T	476	329	202	311	483	370	
	S/T	0.35	0.52	0.40	0.32	0.28	0.40	
	LOC	224	180	175	286	377	-	
	BODY WT. (g)	215	220	215	230	290	205	235
Amphetamine 4 mg/kg	S	758	260	826	386	293	113	683
	E	410	500	580	974	645	289	334
	T	1168	760	1408	1360	938	402	1017
	S/T	0.65	0.34	0.59	0.28	0.31	0.28	0.67
	LOC	311	633	224	451	763	421	65
Amphetamine 16 mg/kg	S	897	1269	1724	1650	2058	487	895
	E	273	160	57	71	190	195	19
	T	1170	1429	1781	1721	2248	682	914
	S/T	0.77	0.89	0.97	0.96	0.92	0.71	0.98
	LOC	45	-	7	21	118	215	43
DA (ng/g)	TUB.	9146	8367	7906	8352	-	5764	9096
	ACC.	9226	9423	7530	8009	10257	6464	9224
	CAUD.	11015	11940	9884	7895	11054	6734	11862
	CORTEX	429	486	116	230	96	91	766
NA (ng/g)	TUB.	265	260	378	410	-	238	403
	ACC.	327	476	1112	941	292	318	629
	CAUD.	83	81	214	186	44	102	105
	CORTEX	738	778	793	888	536	398	725

TUB - Olfactory Tubercles;
ACC - Accumbens Nucleus Sample;
CAUD - Caudate-Putamen Sample.

RAT NO.								
8	9	10	11	12	13	14	15	MEAN ± SEM
129	134	152	102	103	137	116	154	130 ± 7
187	307	243	318	135	229	225	313	238 ± 19
316	441	395	420	238	366	341	467	368 ± 23
0.41	0.30	0.38	0.24	0.43	0.37	0.34	0.33	0.36 ± 0.02
202	254	265	394	167	251	350	415	272 ± 24
205	235	235	240	260	260	245	280	238 ± 7
241	316	193	40	387	156	706	1031	426 ± 78
535	887	764	885	518	305	626	186	563 ± 61
776	1203	957	925	905	461	1332	1217	989 ± 79
0.31	0.26	0.20	0.04	0.43	0.34	0.53	0.85	0.41 ± 0.05
627	394	474	670	545	305	688	199	451 ± 53
	593	1483	1527	2365	1958	2273	2220	1528 ± 161
	262	499	287	43	33	45	63	157 ± 36
	855	1982	1814	2408	1991	2318	2283	1685 ± 150
	0.69	0.75	0.84	0.98	0.98	0.98	0.97	0.88 ± 0.03
	135	263	182	87	26	168	73	106 ± 23
7438	8967	7011	6889	6107	-	4119	6657	7371 ± 413
6979	10507	5958	6405	6344	5578	5600	7178	7645 ± 436
9566	13630	8632	8961	8667	8177	7295	8434	9583 ± 503
219	93	177	81	143	43	103	498	238 ± 54
381	348	297	230	185	-	69	336	292 ± 27
1353	695	650	843	364	674	761	584	668 ± 79
266	106	103	117	76	102	103	125	121 ± 15
313	513	467	410	843	707	571	721	627 ± 47

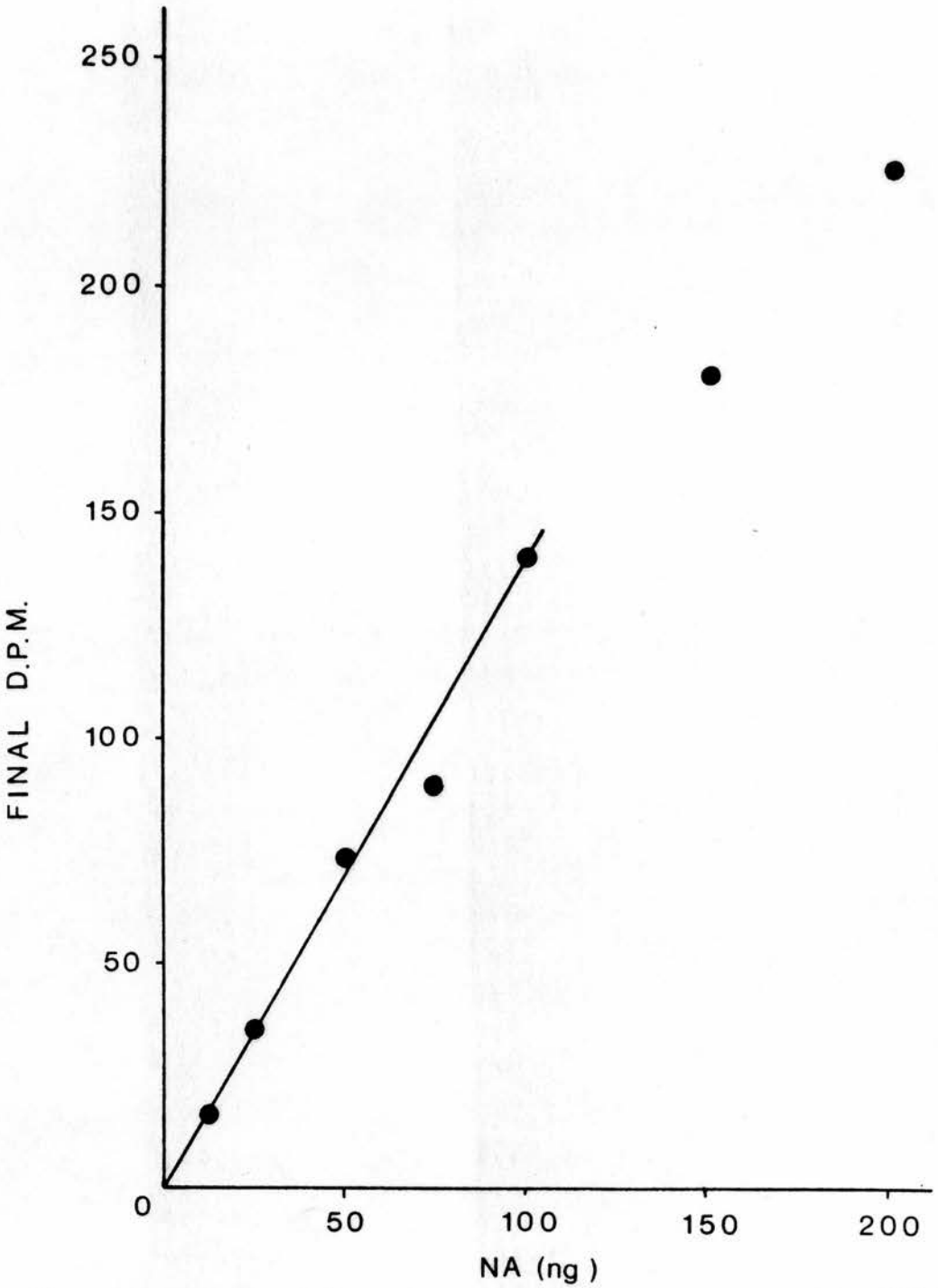


FIG. 41: Standard calibration curve for Noradrenaline(NA) assay. Each point represents mean disintegrations per minute (D.P.M.) x 10^{-3} obtained following assay in duplicate of different amounts of NA added to 300 µl brain tissue extract in 0.1 M perchloric acid (see page 132 and Table 23). The final DPM was obtained by subtracting the DPM produced by tissue extract samples from that of the sample.

The dopamine concentration was about the same, in the region of 7 - 9 ug/g wet weight in all three DA-rich areas assayed - the striatum, nucleus accumbens and olfactory tubercle. There was relatively low variability in the levels found for each area. The estimated dopamine concentrations in the cortex samples were very much lower and these levels showed considerable variation. This variability is probably to be explained by the accidental inclusion, to varying extents, of some tissue from the caudate nucleus in the cortical samples during the dissection; consequently the lower values are probably the more correct estimates. The noradrenaline content of all four areas was much lower, with maximum values in the cortex and accumbens nuclei, followed by the olfactory tubercles, with very low levels being found in the striatum. Variability was quite low.

(iii) Nucleus accumbens lesions (Figs. 42, 43, Table 25). The greatest DA depletion was found in the nucleus accumbens. The olfactory tubercles also showed a marked but less severe fall in DA.

The DA reduction was less in the striatum but even in this area the degree of reduction was considerable (about 40%). Cortical DA content was not affected.

There was a slight though not significant fall ($p > 0.05$) in NA content in the olfactory tubercles. NA content was virtually unchanged in the other areas.

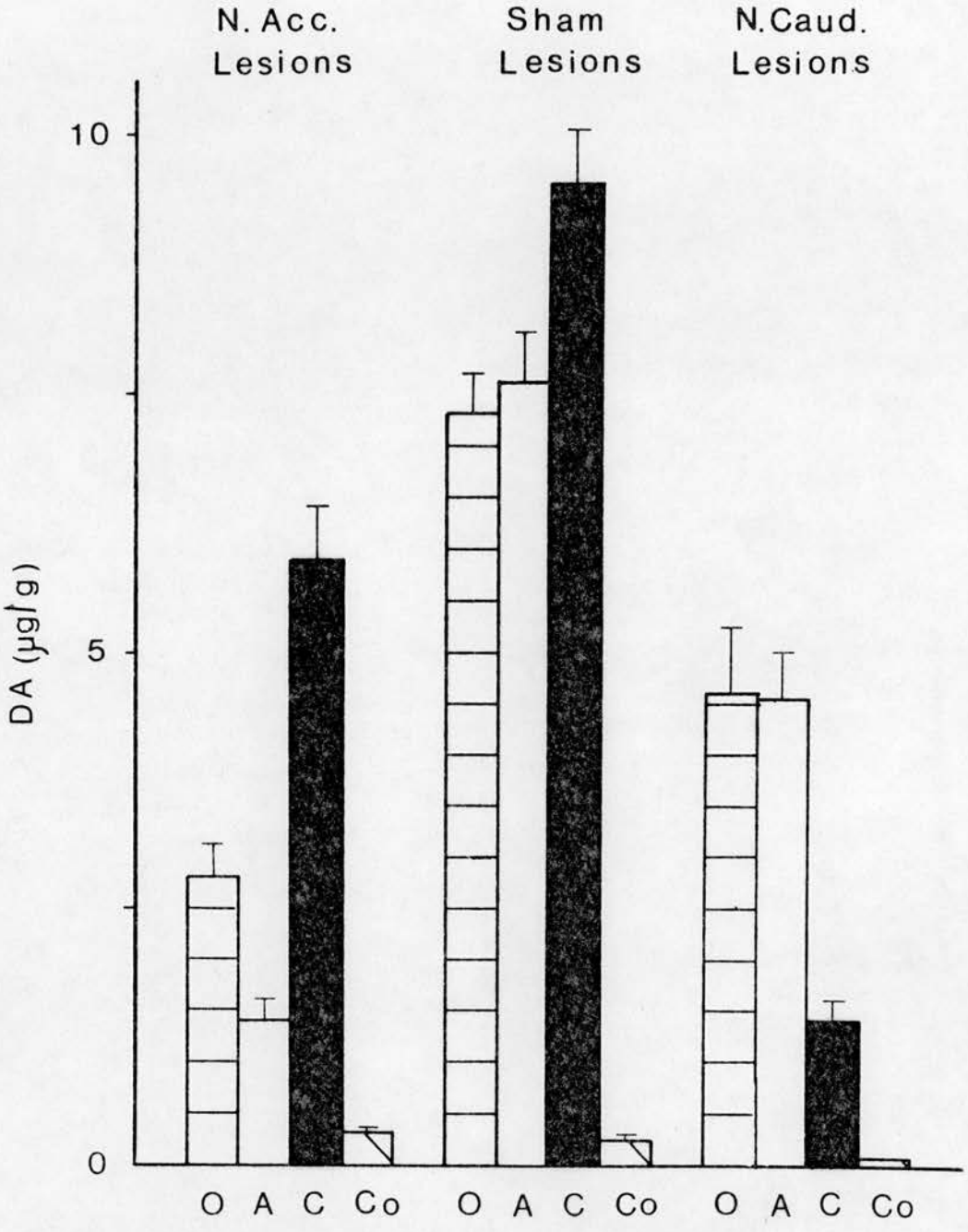


FIG. 42: Dopamine (DA) concentrations in selected brain areas of animals with bilateral "sham" lesions of accumbens nuclei or caudate-putamen nuclei and animals with bilateral 6-hydroxydopamine lesions of the accumbens nuclei (N. Acc.) or caudate-putamen nuclei (N. Caud.). Each column represents mean concentration ± S.E.M. of 13-15 rats.

O - Olfactory Tubercles; A - Accumbens nuclei samples; C - Caudate-putamen samples; Co - Cortical samples.

TABLE 25: Overall behavioural responses in the hole-board apparatus of animals with 6-hydroxydopamine-induced lesions in the accumbens nuclei following administration of 1 ml/kg physiological saline, 4 mg/kg DL-amphetamine sulphate and 16 mg/kg DL-amphetamine sulphate in that order. The treatments were administered at weekly intervals.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

Weight of the animals on the day of the first test is also shown.

At the bottom of the table are given the DA and NA contents of different brain areas.

TREATMENT	ACTIVITY	RAT NO.					
		1	2	3	4	5	6
Saline 1 ml/kg	S	268	46	93	132	119	129
	E	167	90	116	124	200	107
	T	435	136	209	256	319	236
	S/T	0.62	0.34	0.44	0.52	0.37	0.55
	LOC	85	73	112	138	-	95
	BODY WT. (g)	200	210	205	210	260	195
Amphetamine 4 mg/kg	S	389	524	667	307	315	348
	E	150	222	52	188	489	310
	T	539	746	719	495	804	658
	S/T	0.72	0.70	0.93	0.62	0.39	0.53
	LOC	94	162	15	245	588	170
Amphetamine 16 mg/kg	S	1176	1519	817	408	1360	1080
	E	167	49	12	62	89	181
	T	1343	1568	829	470	1449	1261
	S/T	0.88	0.97	0.99	0.87	0.94	0.86
	LOC	119	70	20	109	111	88
DA (ng/g)	TUB.	5383	1820	963	4373	2917	3497
	ACC.	3036	1705	435	1620	1573	1397
	CAUD.	9906	2982	4507	6605	7609	6264
	CORTEX	1016	301	133	530	43	38
NA (ng/g)	TUB.	270	246	171	356	166	177
	ACC.	612	301	1089	999	644	1146
	CAUD.	119	65	115	91	67	105
	CORTEX	489	321	214	166	261	241

*** $p < 0.002$

(Comparison with results from sham-lesioned animals (Table 24) using the Mann-Whitney U-test.)
TUB - Olfactory Tubercles;
ACC - Accumbens Nucleus Sample;
CAUD - Caudate-Putamen Sample.

	RAT NO.							MEAN ± SEM
	7	8	9	10	11	12	13	
	114	198	180	141	128	81	86	132 ± 16
	167	147	159	130	124	79	129	***134 ± 9
	281	345	339	271	252	160	215	266 ± 22
	0.41	0.57	0.53	0.52	0.50	0.51	0.40	***0.48 ± 0.02
	217	201	262	144	253	146	154	***157 ± 18
	210	225	225	230	245	240	225	222 ± 5
	562	703	349	582	908	565	420	511 ± 50
	353	135	333	86	368	59	88	***218 ± 39
	915	838	682	668	1276	624	508	729 ± 57
	0.61	0.84	0.51	0.87	0.71	0.91	0.83	***0.71 ± 0.05
	234	171	311	73	307	44	92	***193 ± 43
	1063	983	1205	900	2290	705	1221	1133 ± 125
	93	41	229	63	36	12	67	85 ± 19
	1156	1024	1434	963	2326	717	1288	1218 ± 128
	0.92	0.96	0.84	0.93	0.98	0.98	0.95	0.93 ± 0.01
	73	44	211	7	48	28	62	76 ± 15
	3121	2818	3125	2694	1103	1991	-	2817 ± 367
	2285	1167	1860	1626	419	670	406	1400 ± 218
	5191	7454	6839	6993	4032	3808	4887	5929 ± 531
	43	100	60	877	225	52	49	267 ± 93
	195	186	163	210	237	269	-	220 ± 17
	442	757	402	1030	212	1128	722	730 ± 91
	102	75	86	63	82	87	70	87 ± 5
	230	702	396	437	321	508	312	354 ± 42

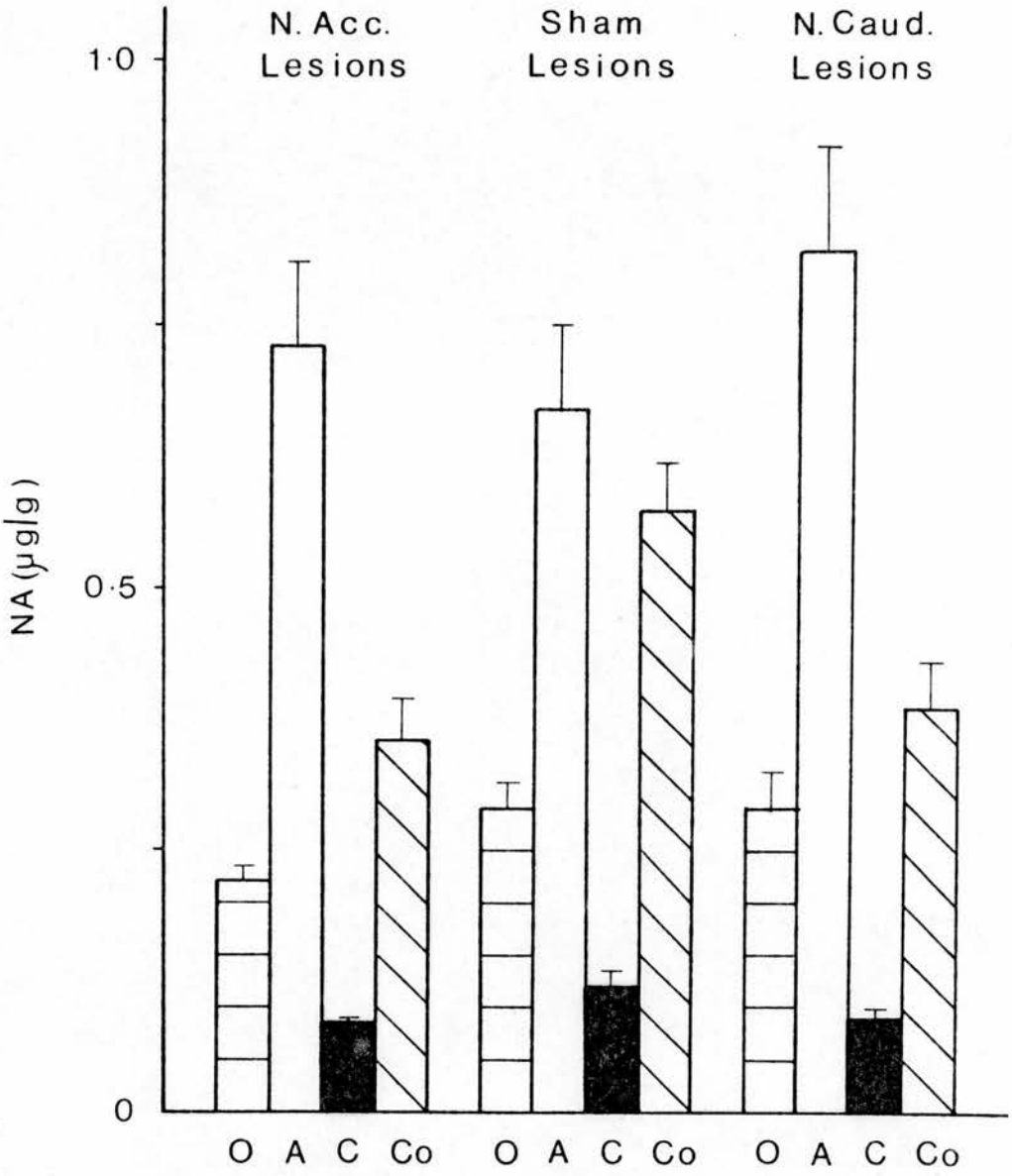


FIG. 43: Noradrenaline (NA) concentrations in selected brain areas of animals with bilateral "sham" lesions of accumbens nuclei or caudate-putamen nuclei and animals with bilateral 6-hydroxydopamine lesions of the accumbens nuclei (N.Acc.) or caudate-putamen nuclei (N.Caud.). Each column represents mean concentration ± S.E.M. of 13-15 rats.

O - Olfactory tubercles; A - Accumbens nuclei samples; C - Caudate-putamen samples; Co - Cortical samples.

(iv) Caudate-putamen lesions (Figs. 42,43, Table 26).

The greatest DA depletion was found in the striatum. Smaller reductions were found in the accumbens nuclei, olfactory tubercles and cortex. Cortical NA levels fell slightly.

(v) Animals with less severe DA depletion

Results are also presented for those animals in which DA depletion did not reach the critical level. Varying degrees of DA depletion are seen, these depletions being greatest in the lesioned areas (Tables, 27, 28).

(b) Behavioural Studies

(i) General behaviour Animals with lesions in the nucleus accumbens were indistinguishable from sham-lesioned controls in appearance, weight and general behaviour by the time of first behavioural testing 10 - 14 days after operation. Animals with lesions in the caudate nuclei tended to be lighter in weight than controls; the weight difference was the greater the more severe the DA depletion achieved (see Table 26). They also tended to be somewhat lethargic and were noted to move around their home cages less.

Significance values quoted in this section refer to comparisons, using the Mann-Whitney test, of the overall responses of the animals in each experimental group during the one hour period of recording with the overall responses in the control group.

TABLE 26: Overall behavioural responses in the hole-board apparatus of animals with 6-hydroxydopamine-induced lesions in the caudate nuclei following administration of 1 ml/kg physiological saline, 4 mg/kg DL-amphetamine sulphate and 16 mg/kg DL-amphetamine sulphate in that order. The treatments were administered at weekly intervals.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

Weight of the animals on the day of the first test is also shown.

At the bottom of the table are given the DA and NA contents of different brain areas.

TREATMENT	ACTIVITY	RAT NO.					
		1	2	3	4	5	6
Saline 1 ml/kg	S	69	21	127	49	85	147
	E	115	56	49	62	90	117
	T	184	77	176	111	175	264
	S/T	0.38	0.27	0.72	0.44	0.49	0.56
	LOC	106	85	84	216	134	288
	BODY WT. (g)	190	150	230	205	220	200
Amphetamine 4 mg/kg	S	57	28	114	55	116	104
	E	270	34	214	206	289	352
	T	327	62	328	261	405	456
	S/T	0.17	0.45	0.35	0.21	0.29	0.23
	LOC	182	588	395	662	434	399
Amphetamine 16 mg/kg	S	127	12	52	31	291	205
	E	666	37	380	283	634	164
	T	793	49	432	314	925	369
	S/T	0.16	0.24	0.12	0.10	0.31	0.56
	LOC	1040	800	-	952	431	291
DA (ng/g)	TUB.	5279	2905	7112	7619	3316	5765
	ACC.	6352	4546	6828	6370	3798	5627
	CAUD.	2359	688	1397	2456	1638	1962
	CORTEX	122	153	63	43	43	61
NA (ng/g)	TUB.	227	623	185	260	262	206
	ACC.	956	1143	554	629	773	333
	CAUD.	74	171	76	54	62	47
	CORTEX	451	525	446	318	252	315

*** $p < 0.002$

* $p < 0.05$

(Comparison with results from sham-lesioned animals (Table 24) using the Mann-Whitney U-test).

TUB - Olfactory Tubercles;
ACC - Accumbens Nucleus Sample;
CAUD - Caudate-Putamen Sample.

	RAT NO.							MEAN ± SEM
	7	8	9	10	11	12	13	
	25	50	54	21	20	18	123	***62 ± 13
	42	35	54	34	26	38	42	***58 ± 8
	67	85	108	55	46	56	165	121 ± 18
	0.37	0.59	0.50	0.38	0.43	0.32	0.74	0.48 ± 0.04
	150	91	196	98	90	56	165	***132 ± 17
	220	220	215	245	195	150	165	200 ± 8
	468	103	8	66	3	33	3	***89 ± 33
	360	319	20	116	8	71	12	***175 ± 37
	828	422	28	182	11	104	15	264 ± 65
	0.57	0.24	0.29	0.36	0.27	0.31	0.20	0.30 ± 0.03
	627	512	355	336	35	1351	39	455 ± 93
	490	185	73	235	29	9	16	***135 ± 40
	130	107	225	178	13	34	6	218 ± 61
	620	292	298	413	42	43	22	355 ± 80
	0.79	0.63	0.24	0.57	0.69	0.20	0.72	0.41 ± 0.07
	51	106	131	441	21	1986	24	*523 ± 169
	1978	-	6533	7367	3149	2999	1241	4605 ± 651
	2609	4395	3890	6515	3371	3375	1747	4571 ± 454
	1578	1679	1486	1446	1086	433	135	1411 ± 190
	61	63	64	43	68	84	102	75 ± 9
	213	-	290	364	250	335	243	288 ± 34
	350	523	1361	584	1166	1416	852	818 ± 101
	52	77	62	108	166	113	128	92 ± 11
	543	674	230	561	321	202	184	386 ± 44

TABLE 27: Overall behavioural responses in the hole-board apparatus of animals with 6-hydroxydopamine-induced lesions in the accumbens nuclei which did not produce adequate degrees of DA depletion (see page 131) following administration of 1 ml/kg physiological saline, 4 mg/kg DL-amphetamine sulphate and 16 mg/kg DL-amphetamine sulphate in that order. The treatments were administered at weekly intervals.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

Weight of the animals on the day of the first test is also shown.

At the bottom of the table are given the DA and NA contents of different brain areas.

TREATMENT	ACT-IVITY	RAT NO. 1	2	3	4	5	6	7	MEAN ± SEM
Saline 1 ml/kg	S	138	155	179	125	80	170	98	135 ± 14
	E	155	209	375	282	132	170	134	208 ± 34
	T	293	364	554	407	212	340	232	343 ± 44
	S/T	0.47	0.43	0.32	0.31	0.38	0.50	0.42	0.40 ± 0.03
	LOC	186	250	279	359	-	98	340	252 ± 40
	BODY WT(g)	220	245	260	245	190	230	225	231 ± 9
Amphet. 4 mg/kg	S	337	141	594	105	222	855	284	363 ± 103
	E	307	95	576	538	219	883	376	428 ± 100
	T	644	236	1170	643	441	1738	660	790 ± 192
	S/T	0.52	0.59	0.51	0.16	0.50	0.49	0.43	0.46 ± 0.05
	LOC	258	113	253	869	301	647	197	377 ± 104
Amphet. 16 mg/kg	S	920	1011	548	1689	216	1077	1901	1052 ± 224
	E	513	55	281	137	46	114	118	181 ± 63
	T	1433	1066	829	1826	262	1191	2019	1232 ± 226
	S/T	0.64	0.94	0.66	0.92	0.82	0.90	0.94	0.83 ± 0.05
	LOC	-	88	136	111	107	44	132	103 ± 14
DA (ng/g)	TUB.	7792	2913	6376	4706	2878	2764	4624	4579 ± 826
	ACC.	4638	3287	6248	4004	2395	2539	3294	3772 ± 507
	CAUD.	11432	16583	11931	10792	5236	-	8058	10672 ± 1563
	CORTEX	533	58	184	63	90	75	71	153 ± 66
NA (ng/g)	TUB.	296	255	182	213	218	161	214	220 ± 17
	ACC.	1130	702	751	552	711	543	854	749 ± 77
	CAUD.	50	108	98	79	102	-	117	92 ± 10
	CORTEX	489	376	394	375	401	507	594	448 ± 32

TUB - Olfactory Tubercles; ACC - Nucleus accumbens sample;
CAUD - Caudate-putamen sample.

TABLE 28: Overall behavioural responses in the hole-board apparatus of animals with 6-hydroxydopamine-induced lesions in the caudate nuclei which did not produce adequate degrees of DA depletion (see page131) following administration of 1 ml/kg physiological saline, 4 mg/kg DL-amphetamine sulphate and 16 mg/kg DL-amphetamine sulphate in that order. The treatments were administered at weekly intervals.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

Weight of the animals on the day of the first test is also shown.

At the bottom of the table are given the DA and NA contents of different brain areas.

TREATMENT	ACTIVITY	RAT NO. 1	2	3	4	5	6	MEAN ± SEM
Saline 1 ml/kg	S	61	167	98	73	77	95	95 ± 15
	E	137	149	50	69	81	98	97 ± 15
	T	198	316	148	142	158	193	192 ± 26
	S/T	0.31	0.53	0.66	0.51	0.49	0.49	0.50 ± 0.05
	LOC	301	133	100	73	124	133	144 ± 33
	BODY WT.(g)	185	185	220	225	245	240	217 ± 11
Amphet. 4 mg/kg	S	320	410	209	1104	-	673	543 ± 160
	E	462	786	346	491	-	267	470 ± 111
	T	782	1196	555	1595	-	940	1014 ± 179
	S/T	0.41	0.34	0.38	0.69	-	0.72	0.51 ± 0.08
	LOC	624	319	410	-	-	203	389 ± 89
Amphet. 16 mg/kg	S	535	1443	1274	1176	1263	1151	1140 ± 128
	E	172	234	252	25	29	49	127 ± 43
	T	707	1677	1526	1201	1292	1200	1267 ± 137
	S/T	0.76	0.86	0.83	0.98	0.98	0.96	0.89 ± 0.04
	LOC	218	114	183	95	46	40	116 ± 30
DA (ng/g)	TUB.	7695	6713	5839	6142	6021	6801	6535 ± 278
	ACC.	5450	5451	6182	5981	5738	6280	5847 ± 147
	CAUD.	3026	5215	3990	4395	5034	8989	5108 ± 840
	CORTEX	84	55	61	63	58	58	63 ± 4
NA (ng/g)	TUB.	243	324	214	181	223	253	240 ± 20
	ACC.	811	1125	767	523	590	986	800 ± 93
	CAUD.	121	156	109	77	133	208	134 ± 18
	CORTEX	388	759	384	467	501	571	512 ± 57

TUB - Olfactory Tubercles; ACC - Nucleus accumbens sample; CAUD - Caudate-putamen sample.

(ii) Behaviour following an injection of 1 ml/kg saline (Figs. 44,45, Tables 24-26, 29).

Compared with sham-lesioned controls, animals with lesions in the accumbens nuclei showed a reduction in exploratory dipping ($p < 0.002$) with "stereotyped" dipping remaining at around control levels. The S/T ratio was therefore increased ($p < 0.002$). Locomotor counts were also reduced ($p < 0.002$).

Animals with lesions of the caudate-putamen showed a general reduction in both forms of dipping as well as locomotor counts. It was found that this behavioural reduction was most marked in those animals which proved to have most severe DA depletions and which usually were the most ill-looking and cachectic. The reductions in levels of stereotyped and exploratory dipping as well as locomotor counts were statistically significant ($p < 0.002$) in all three cases. The increases in S/T ratio were not significant.

(iii) Behaviour following an injection of DL-amphetamine sulphate 4 mg/kg (Figs. 46, 47, Tables 24-26,30).

In comparison with sham-lesioned controls, animals with lesions of the accumbens nuclei showed a marked reduction in exploratory dipping ($p < 0.002$) compared with sham-lesioned controls. "Stereotyped" dipping levels were unchanged and the S/T ratio was increased ($p < 0.002$). Locomotor counts also decreased markedly ($p < 0.002$).

TABLE 29: Behaviour in the hole-board apparatus of rats with "sham" lesions of caudate or accumbens nuclei and of rats with 6-hydroxydopamine lesions of the accumbens or caudate nuclei following administration of 1 ml/kg saline i.p. Figures show mean activity ± S.E.M. during successive 10 min. intervals after injection.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts. 13-15 rats in each group.

TIME INTERVAL (min)	0 - 10			10 - 20		
LESION	S	E	LOC	S	E	LOC
Sham	23 ± 2	70 ± 3	82 ± 6	22 ± 2	45 ± 5	49 ± 7
N. Acc.	22 ± 3	54 ± 3	61 ± 7	22 ± 2	26 ± 4	27 ± 5
N. Caud.	11 ± 2	23 ± 3	51 ± 6	8 ± 2	8 ± 2	29 ± 8
TIME INTERVAL (min)	20 - 30			30 - 40		
LESION	S	E	LOC	S	E	LOC
Sham	24 ± 2	39 ± 5	36 ± 6	20 ± 2	37 ± 4	50 ± 8
N. Acc.	22 ± 3	16 ± 2	16 ± 4	21 ± 3	14 ± 1	17 ± 3
N. Caud.	9 ± 3	6 ± 1	12 ± 3	12 ± 3	7 ± 1	13 ± 2
TIME INTERVAL (min)	40 - 50			50 - 60		
LESION	S	E	LOC	S	E	LOC
Sham	21 ± 3	30 ± 4	36 ± 4	19 ± 3	17 ± 4	24 ± 6
N. Acc.	23 ± 3	12 ± 1	20 ± 4	22 ± 3	12 ± 2	16 ± 3
N. Caud.	12 ± 3	7 ± 2	19 ± 6	10 ± 2	7 ± 2	9 ± 3

Details of individual rat responses can be found in the Appendix, Tables 25 - 27.

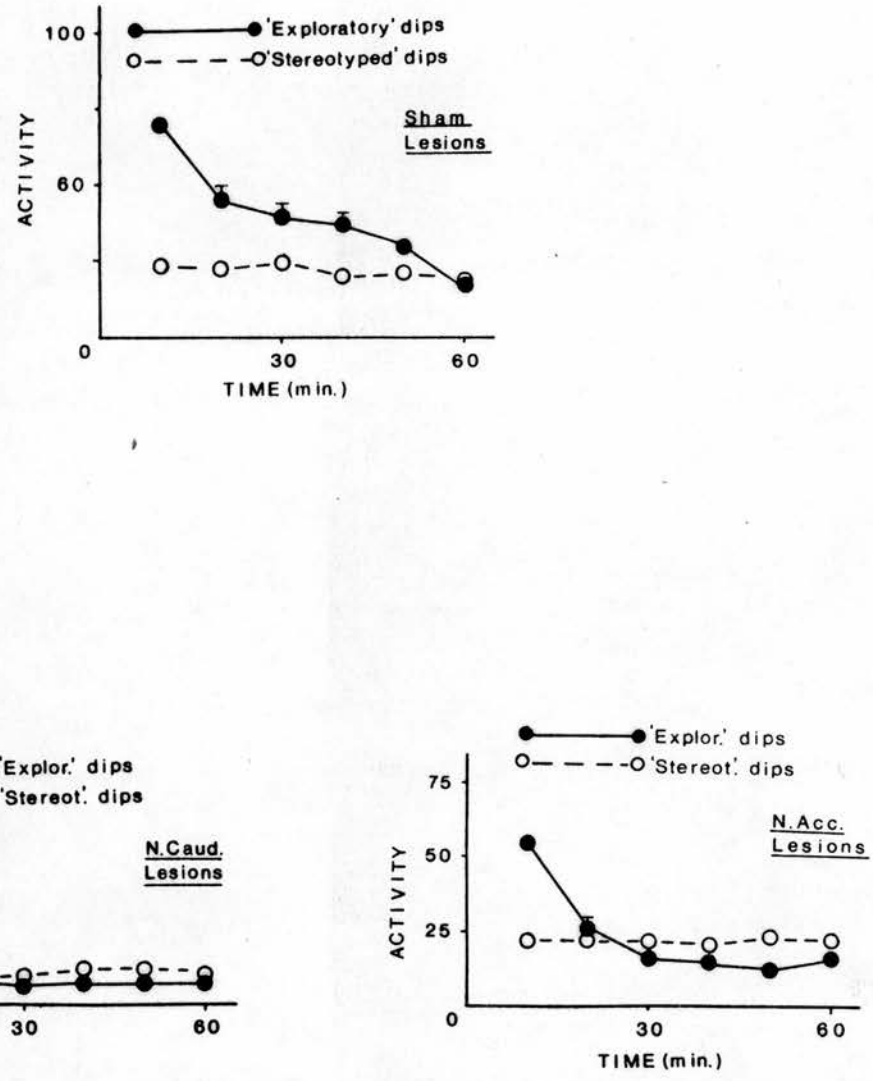


FIG. 44: Behavioural response in the hole-board apparatus by animals with (a) Bilateral "sham" lesions of accumbens nuclei or caudate-putamen nuclei or of animals with (b) bilateral 6-hydroxydopamine lesions of the caudate-putamen nuclei (N.Caud.) or (c) the accumbens nuclei (N.Acc.) following i.p. administration of 1 ml/kg saline. Each point represents mean activity ± S.E.M. during successive 10 min. intervals after the injection of 13-15 animals.

TABLE 30: Behaviour in the hole-board apparatus of rats with "sham" lesions of caudate or accumbens nuclei and of rats with 6-hydroxydopamine lesions of the accumbens or caudate nuclei following administration of 4 mg/kg DL-amphetamine sulphate i.p. Figures show mean activity ± S.E.M. during successive 10 min. intervals after injection of 13-15 rats.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts.

TIME INTERVAL (min)	0 - 10			10 - 20		
LESION	S	E	LOC	S	E	LOC
Sham	20 ± 4	67 ± 7	63 ± 8	31 ± 5	88 ± 9	65 ± 8
N. Acc.	27 ± 4	42 ± 4	42 ± 6	63 ± 12	30 ± 5	31 ± 7
N. Caud.	9 ± 2	23 ± 5	55 ± 9	9 ± 2	29 ± 6	71 ± 11
TIME INTERVAL (min)	20 - 30			30 - 40		
LESION	S	E	LOC	S	E	LOC
Sham	59 ± 13	95 ± 10	81 ± 12	87 ± 19	104 ± 17	88 ± 12
N. Acc.	88 ± 9	38 ± 7	25 ± 6	103 ± 7	44 ± 11	28 ± 10
N. Caud.	14 ± 5	29 ± 6	77 ± 14	17 ± 7	32 ± 7	89 ± 23
TIME INTERVAL (min)	40 - 50			50 - 60		
LESION	S	E	LOC	S	E	LOC
Sham	107 ± 20	105 ± 19	76 ± 13	123 ± 25	105 ± 18	86 ± 15
N. Acc.	108 ± 11	37 ± 9	30 ± 9	117 ± 15	27 ± 8	35 ± 9
N. Caud.	20 ± 9	31 ± 7	83 ± 25	20 ± 10	30 ± 7	79 ± 27

Details of individual rat responses can be found in the Appendix, Tables 28 - 30.

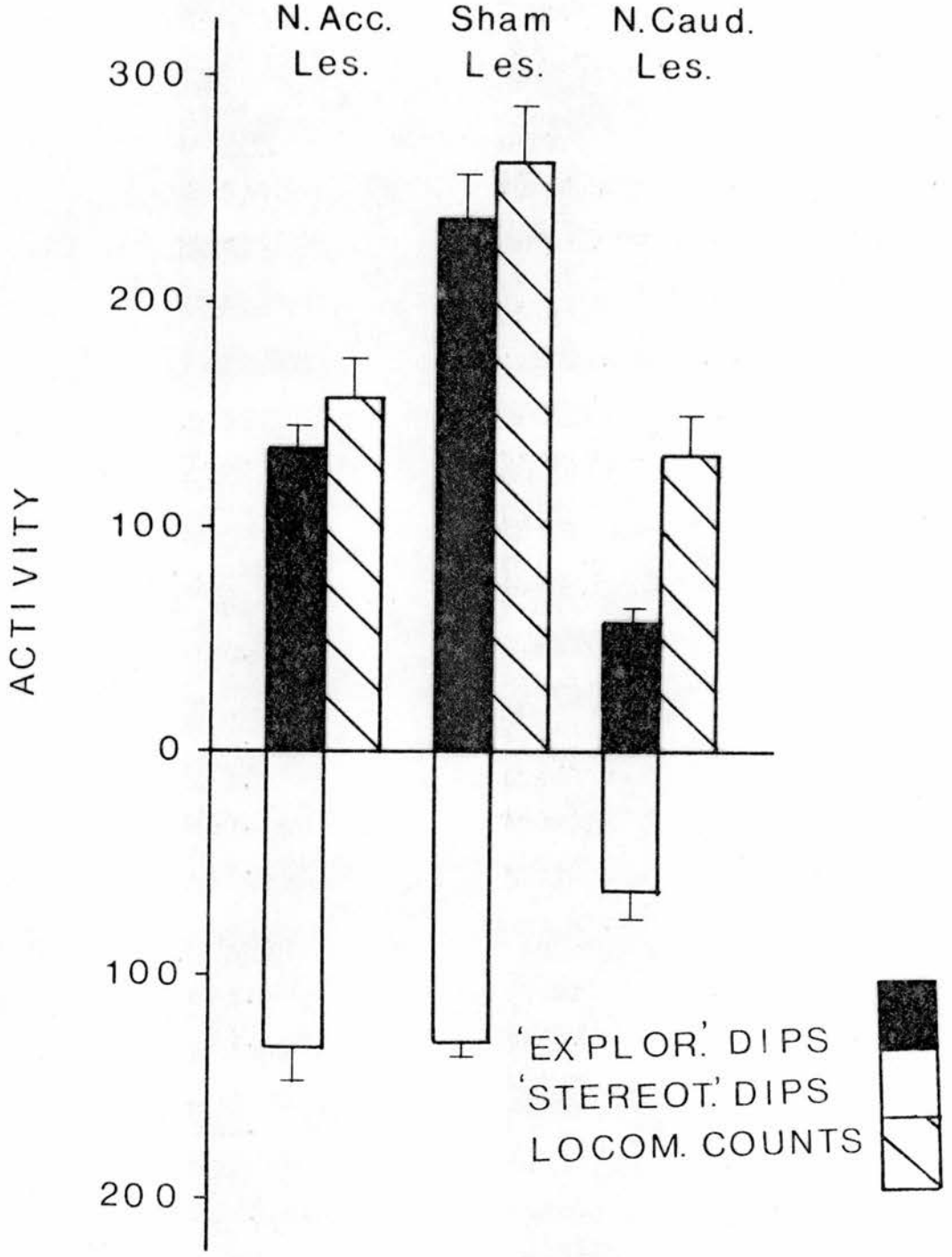


FIG. 45: Overall behavioural response in the hole-board apparatus following i.p. administration of 1 ml/kg saline by animals with (a) 6-hydroxydopamine lesions of the accumbens nuclei (N.Acc.Les.) (b) sham lesions of the accumbens or caudate-putamen nuclei (Sham Les.) and (c) 6-hydroxydopamine lesions of the caudate-putamen nuclei (N. Caud. Les.). Each column represents mean activity ± S.E.M. of 13-15 rats during a one hour period immediately after the injection.

Animals with lesions of the caudate nuclei showed a marked decrease in "stereotyped" dipping ($p < 0.002$) as well as in "exploratory" dipping ($p < 0.002$). Locomotor counts were unaffected. The S/T ratio was reduced, though this was not statistically significant.

The marked variation in the results from animals with lesions in the caudate nuclei is accounted for by the fact that some of the animals with the more severe degrees of DA depletion showed virtually no behavioural response to amphetamine at all (Animals 11 and 13, Table 26) whereas certain others, again with the more severe degrees of DA depletion, responded with a considerable locomotor stimulation without much "exploratory" dipping (Animals 2 and 12).

(iv) Behaviour following an injection of 16 mg/kg DL-amphetamine sulphate (Figs. 48,49,Tables 24-26, 31). The behavioural differences between animals with lesions in the accumbens nuclei and sham-lesioned animals were not marked. There were slight reductions in "exploratory" dipping and locomotor responses which were not statistically significant. N. accumbens-lesioned animals tended to enter the "stereotyped" dipping phase sooner and this was then more rapidly joined and then replaced by "non-dipping stereotyped behaviour", which appeared to be more intense. This accounts for the slight reduction (not statistically significant)

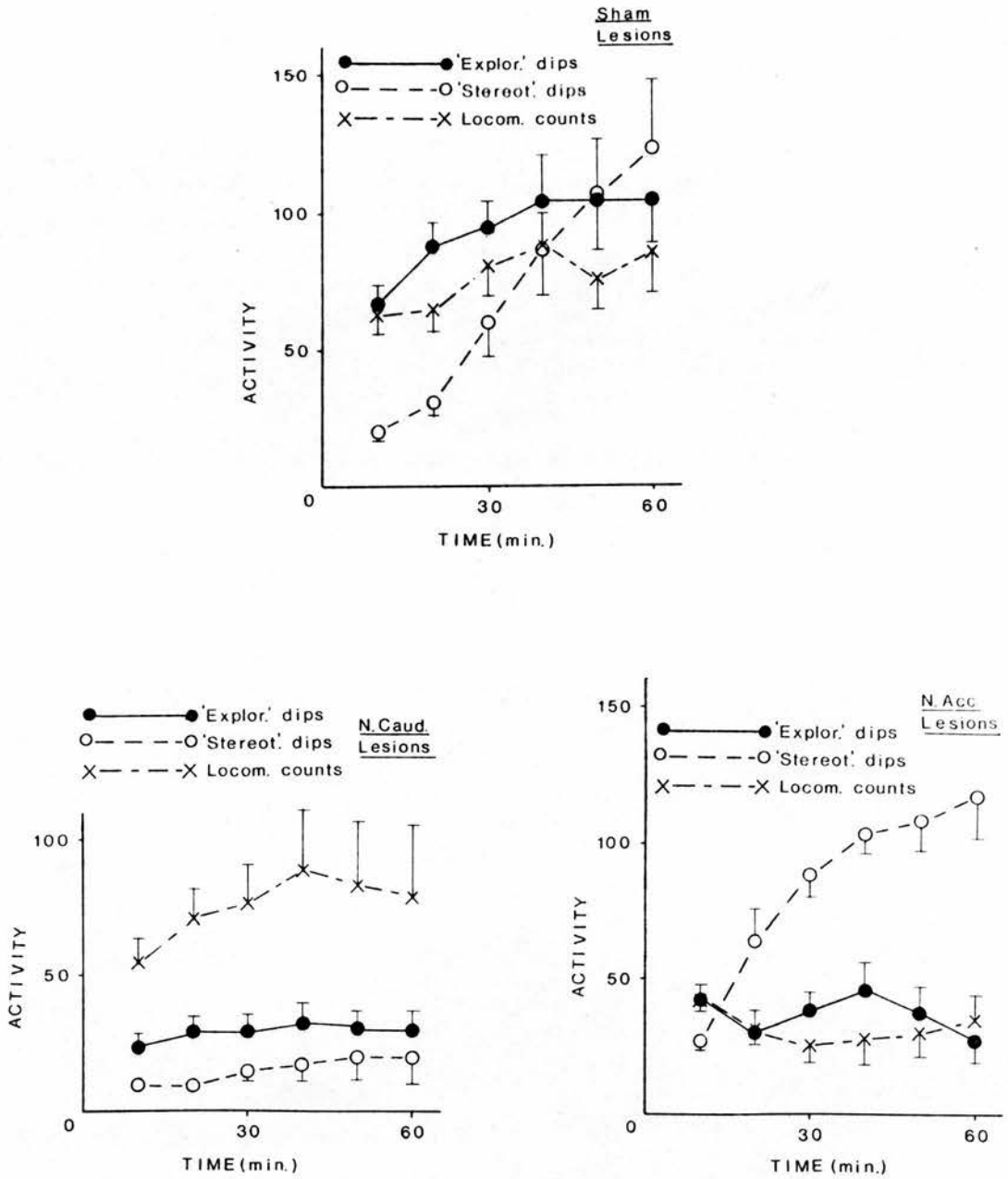


FIG. 46: Behavioural response in the hole-board apparatus by animals with (a) bilateral "sham" lesions of accumbens nuclei or caudate-putamen nuclei or of animals with (b) bilateral 6-hydroxydopamine lesions of the caudate-putamen (N.Caud.) or (c) the accumbens nuclei (N.Acc.) following i.p. administration of 4 mg/kg DL-amphetamine sulphate. Each point represents mean activity ± S.E.M. during successive 10 min. intervals after the injection of 13-15 animals.

TABLE 31: Behaviour in the hole-board apparatus of rats with "sham" lesions of caudate or accumbens nuclei and of rats with 6-hydroxydopamine lesions of the accumbens or caudate nuclei following administration of 16 mg/kg DL-amphetamine sulphate i.p. Figures show mean activity ± S.E.M. during successive 10 min. intervals after injection of 13-15 rats.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts.

TIME INTERVAL (min)	0 - 10			10 - 20		
LESION	S	E	LOC	S	E	LOC
Sham	109 ± 18	64 ± 9	54 ± 11	408 ± 51	33 ± 15	19 ± 9
N. Acc.	145 ± 22	53 ± 7	54 ± 8	*285 ± 39	15 ± 7	10 ± 5
N. Caud.	17 ± 6	35 ± 7	82 ± 26	26 ± 8	39 ± 9	89 ± 24
TIME INTERVAL (min)	20 - 30			30 - 40		
LESION	S	E	LOC	S	E	LOC
Sham	*384 ± 42	30 ± 12	11 ± 6	**283 ± 50	15 ± 6	6 ± 3
N. Acc.	**226 ± 43	9 ± 4	5 ± 3	**176 ± 38	3 ± 2	3 ± 2
N. Caud.	18 ± 4	40 ± 12	79 ± 28	26 ± 8	36 ± 12	81 ± 28
TIME INTERVAL (min)	40 - 50			50 - 60		
LESION	S	E	LOC	S	E	LOC
Sham	**224 ± 42	9 ± 4	6 ± 3	**113 ± 34	5 ± 3	11 ± 7
N. Acc.	**196 ± 43	4 ± 3	3 ± 2	**110 ± 40	1 ± 1	1 ± 1
N. Caud.	24 ± 7	39 ± 14	89 ± 31	25 ± 11	30 ± 11	86 ± 31

Details of individual rat responses can be found in the Appendix, Tables 31 - 33.

* Non-dipping stereotyped behaviour (see page 146).

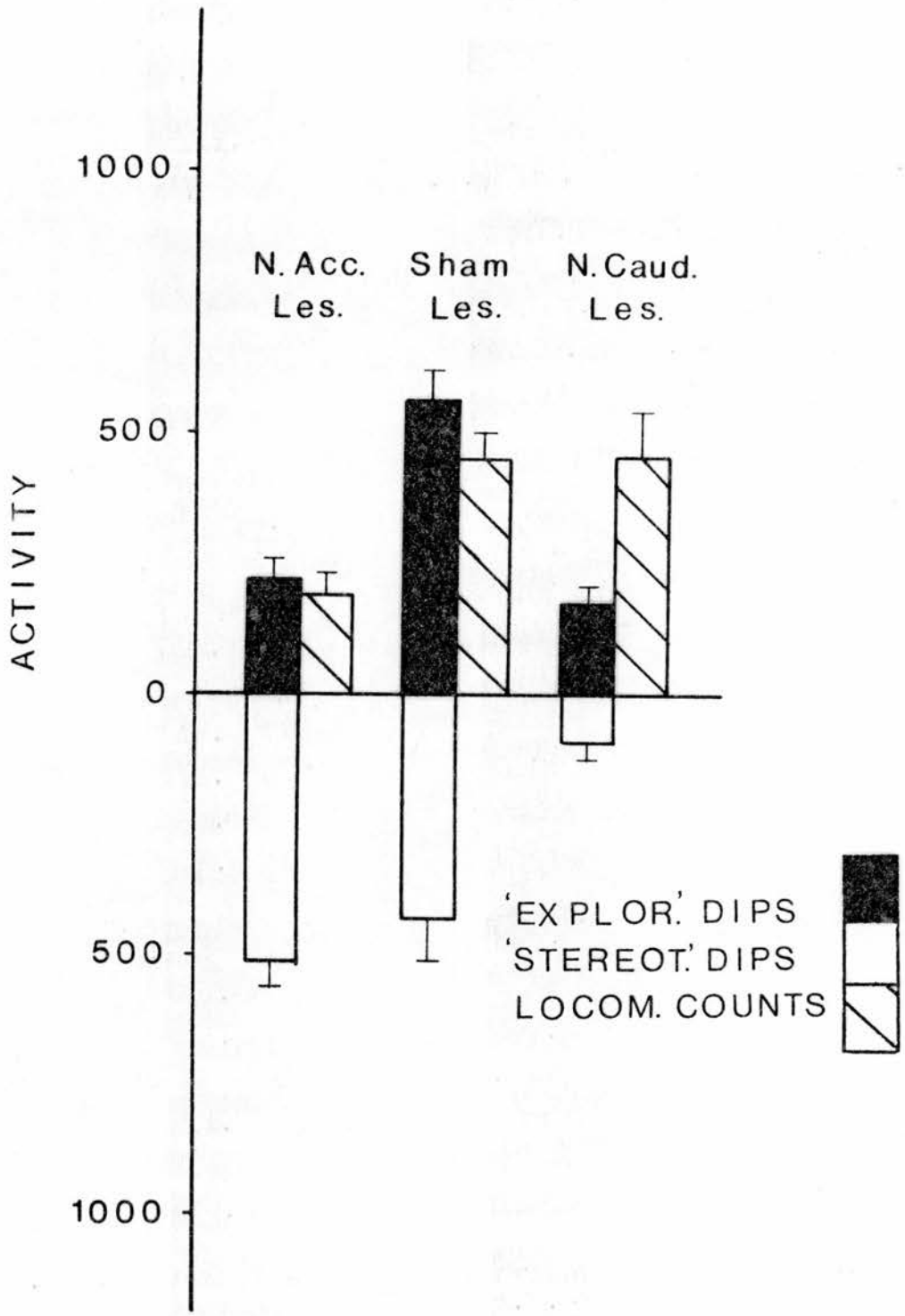


FIG.47: Overall behavioural response in the hole-board apparatus following i.p. administration of 4 mg/kg DL-amphetamine sulphate by animals with (a) 6-hydroxydopamine lesions of the accumbens nuclei (N.Acc.Les.),(b) sham lesions of the accumbens or caudate-putamen nuclei (Sham Les.) and (c) 6-hydroxydopamine lesions of the caudate-putamen nuclei (N.Caud.Les.). Each column represents mean activity ± S.E.M. of 13-15 rats during a one hour period immediately after the injection.

in "stereotyped" dipping also observed. The S/T ratio was increased (not statistically significant). Sniffing appeared markedly reduced.

"Non-dipping stereotyped behaviour" consisted of intense, rapid, repetitive head movements which on the hole-board occurred in relationship to the holes although in certain cases with extreme stimulation this behaviour was observed also to take place between the holes (Makanjuola et al. 1977b). The phenomenon involved up and down as well as side to side movements of the head which at first accompanied "stereotyped" dipping and then gradually replaced this dipping behaviour, the up and down movements being too shallow to be recorded as hole-dips. Therefore, as the "non-dipping stereotyped behaviour" became more intense 'stereotyped' dipping gradually fell off (Fig. 48). Intense gnawing and biting at the hole-edges accompany the head movements and in intact or sham-lesioned animals intense sniffing also occurred, although, as has been mentioned above, sniffing did not feature in the animals with 6-OHDA lesions of the nucleus accumbens.

Animals with lesions in the caudate nuclei behaved markedly differently from sham-lesioned controls or animals with lesions in the accumbens nuclei. In these animals the most prominent feature was a marked reduction of "stereotyped" dipping compared with sham-lesioned controls ($p < 0.002$). "Non-dipping stereotyped behaviour" was never

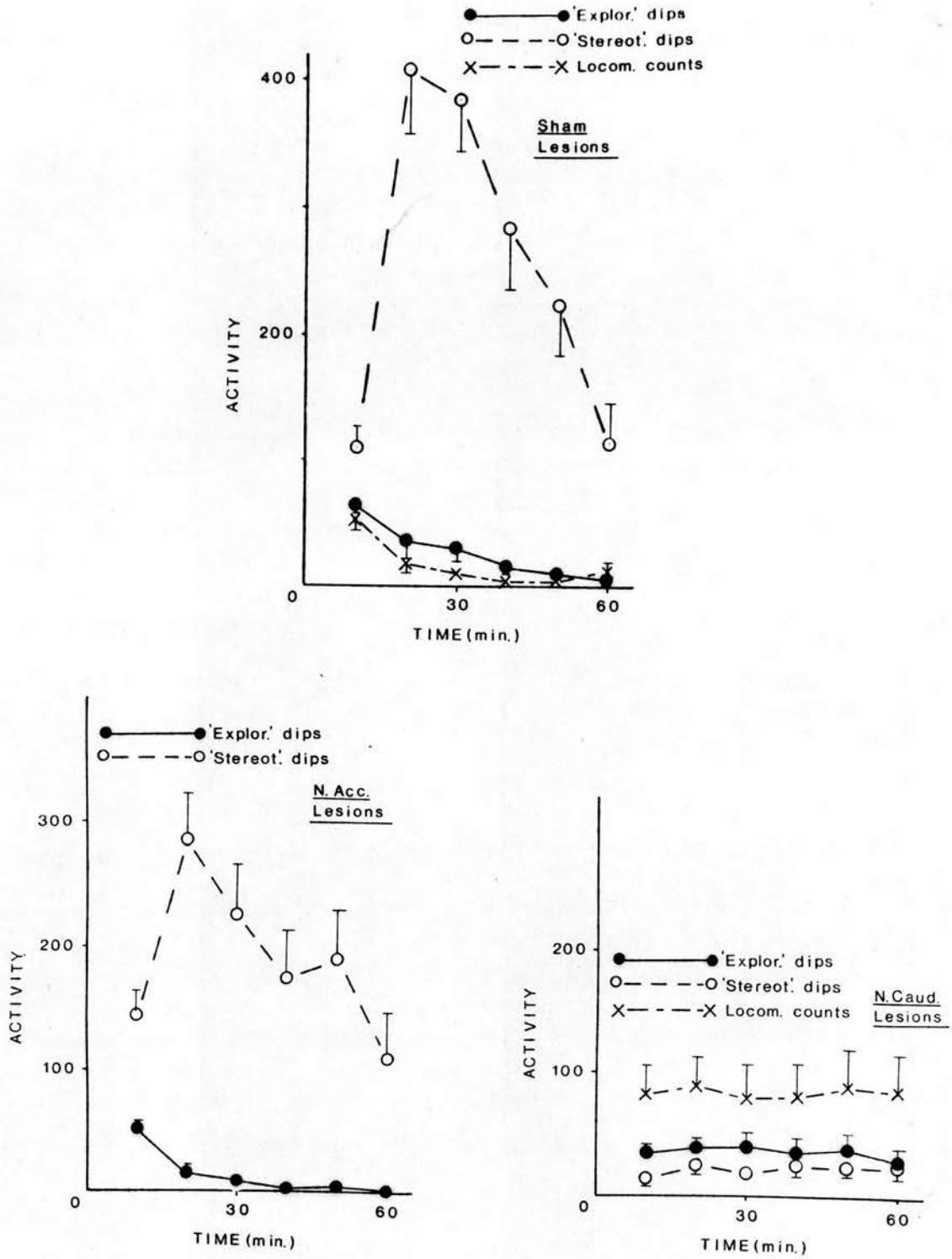


FIG. 48: Behavioural response in the hole-board apparatus by animals with (a) bilateral "sham" lesions of accumbens nuclei or caudate-putamen nuclei or of animals with (b) bilateral 6-hydroxydopamine lesions of the caudate-putamen nuclei (N.Caud.) or (c) the accumbens nuclei (N.Acc.) following i.p. administration of 16 mg/kg DL-amphetamine sulphate. Each point represents mean activity ± S.E.M. during successive 10 min. intervals after the injection of 13-15 animals. "Non-dipping stereotyped behaviour" (see page 146) accounts for the apparent fall in the level of "stereotyped" dipping in the latter half of the experimental period in the sham lesioned and accumbens-lesioned animals.

observed. There was a moderate stimulation of "exploratory" dipping (not statistically significant) and a greater stimulation of locomotor activity ($p < 0.05$ for locomotor counts). Intense sniffing was observed. The majority of animals moved continually around the hole-board, sniffing continuously and dipping occasionally. Again there was a marked variance in the results which made interpretation somewhat difficult. As with the response to 4 mg/kg DL-amphetamine sulphate, the same animals with severe DA depletions showed no or relatively little locomotor or hole-dipping response whatsoever to the drug whereas two responded with a marked stimulation of locomotor activity (Animals 2,11,12,13; Table 26). Intense sniffing was observed even in these animals, however.

2. Effects of electrolytic lesions of the nucleus accumbens septi on behaviour following saline and amphetamine administration

(a) Extent of lesion Lesions of various size were achieved with current doses of 30-60 mC. Generally an oval lesion was obtained, the elongation being in the dorso-ventral direction (Figs. 50,51). The dorsal aspect of the lesion was continuous with the electrode needle track, which itself was surrounded by an area of damage too wide to be accounted for by physical passage of the electrode per se. Needle tracks in sham-operated animals (in which no current was passed) were much less conspicuous

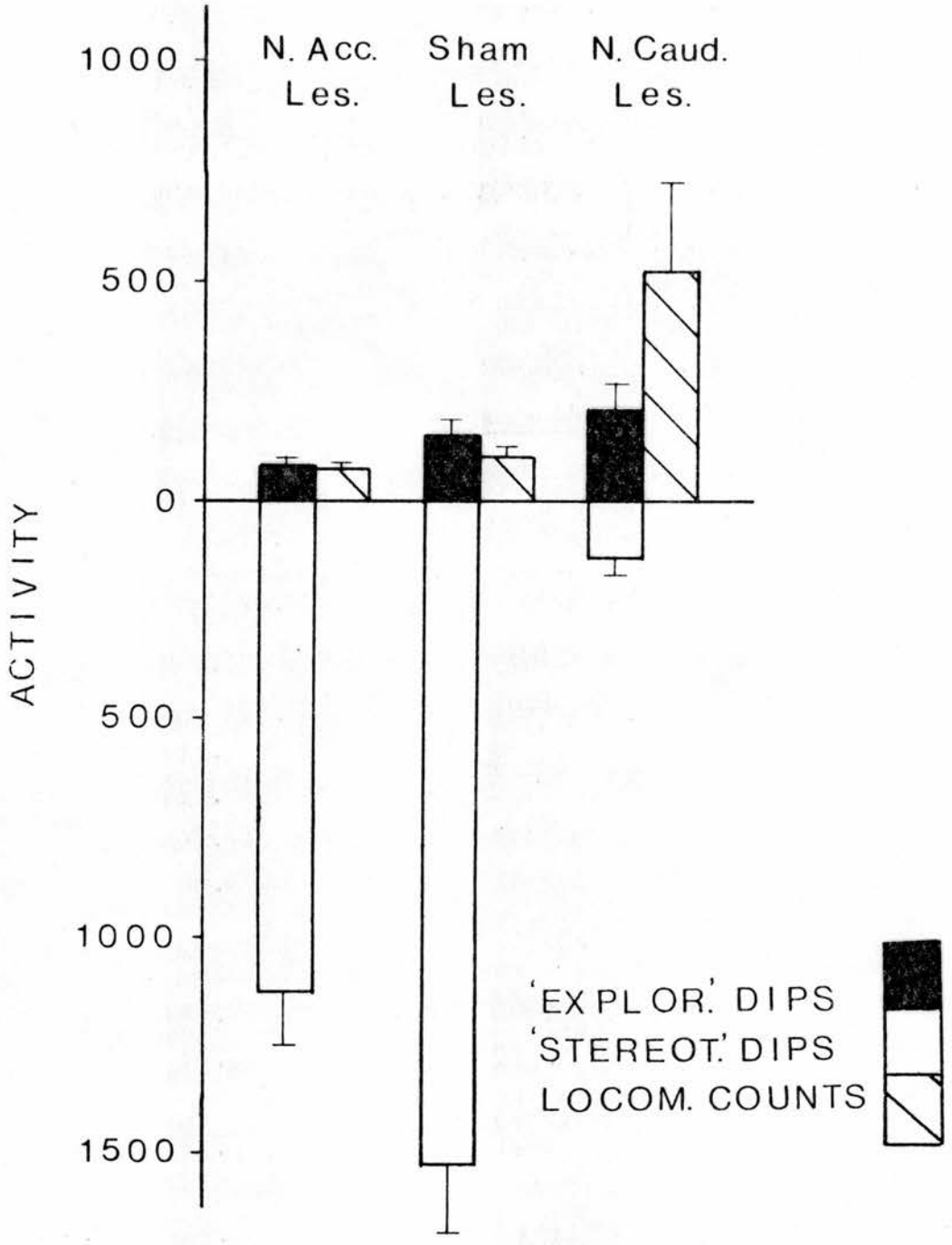


FIG. 49: Overall behavioural response in the hole-board apparatus following i.p. administration of 16 mg/kg DL-amphetamine sulphate by animals with (a) 6-hydroxydopamine lesions of the accumbens nuclei (N.Acc.Les.), (b) sham lesions of the accumbens or caduate-putamen nuclei (Sham Les.) and (c) 6-hydroxydopamine lesions of the caudate-putamen nuclei (N. Caud.Les.). Each column represents mean activity ± S.E.M. of 13-15 rats during a one hour period immediately after the injection.

(Fig. 50d). This damage around the needles was therefore probably caused by passage of current around the needle, between the two electrodes. In addition to damage to the accumbens nucleus itself, neighbouring structures were also damaged to some degree. The anterior commissure which passes through the lateral aspect of the nucleus, was invariably destroyed. The olfactory tubercle, anterior olfactory nucleus, lateral ventricle and ventro-medial aspect of the anterior part of the caudate nucleus were often damaged to some degree. Animals in which damage to these structures (apart from the anterior commissure) especially the caudate nucleus, was thought to be more than minimal, were excluded from final analysis. Results are presented for those animals in which greater than 50% of the accumbens nucleus was destroyed.

(b) General condition and behaviour Even with the most extreme lesions of the nucleus accumbens the animals appeared perfectly normal at the first behavioural testing 10-14 days after operation. Weight gain continued normally and the animals in all respects were indistinguishable from sham-lesioned controls on inspection.

Ten to fourteen days after operation each animal was studied for one hour on the hole-board following administration of 1 ml/kg saline i.p. Seven days later the animal was again studied following 4 mg/kg DL-amphetamine sulphate and, after another seven days, 16 mg/kg DL-amphetamine sulphate. The illumination of the chamber was increased during the last study (i.e. after administration of 16 mg/kg amphetamine) so that "non-dipping

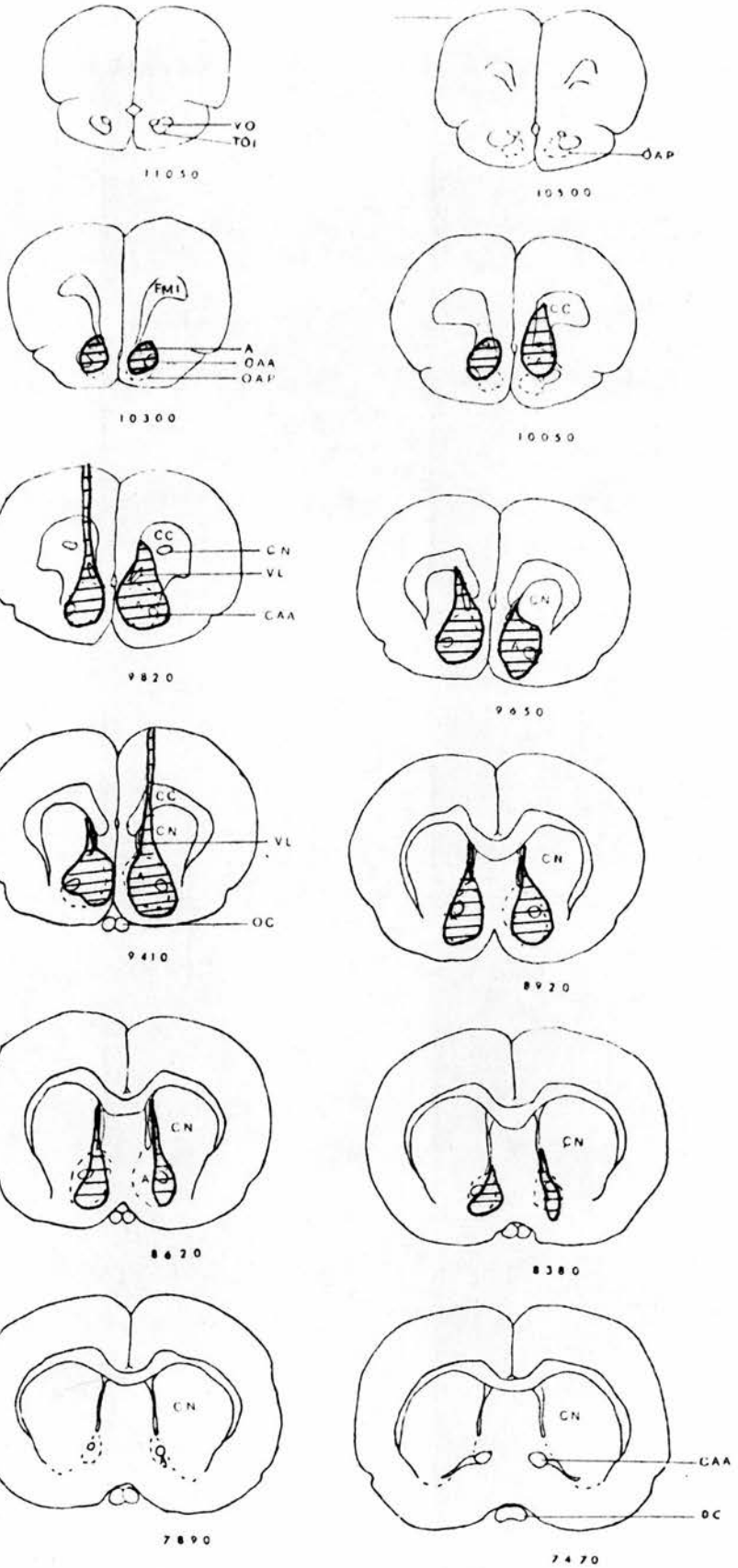
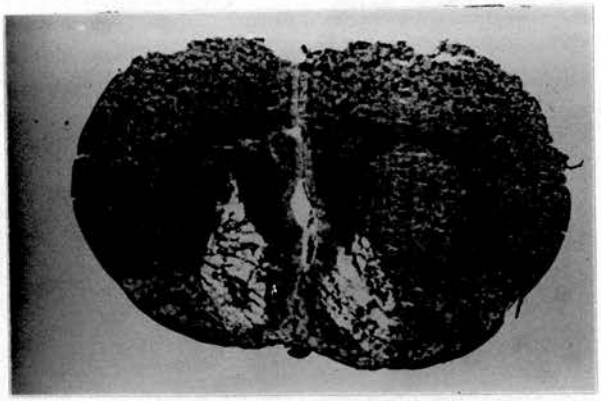
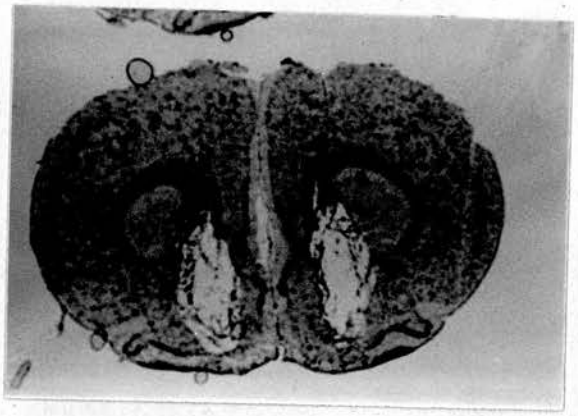


FIG. 50: Scale drawings of sections of the rat brain adapted from the Atlas of König and Klippel (1963) - see page 70. The appearance of bilateral electrolytic lesions of the accumbens nuclei at different antero-posterior coordinates is shown. These coordinates are denoted below each figure in microns in accordance with the atlas of Konig and Klippel. VO - olfactory ventricle; TOI - intermediate olfactory track; OAP - Anterior olfactory nucleus; CAA - anterior commissure; CC - corpus callosum; A - accumbens nucleus; CN - caudate-putamen; OC - optic chiasma.



a



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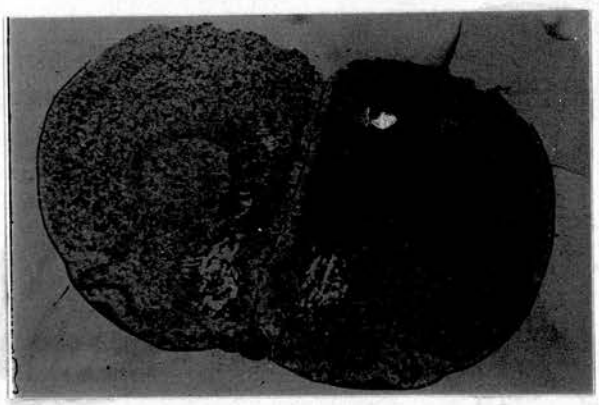

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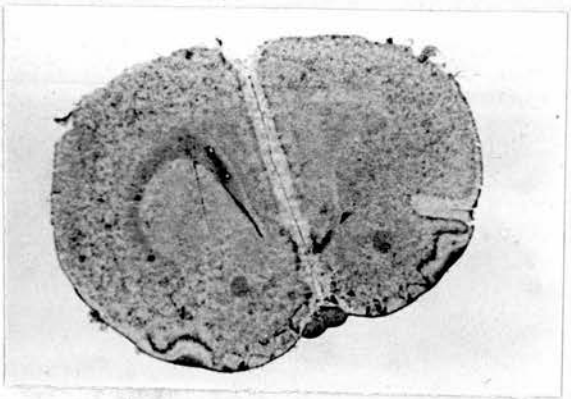


d

FIG. 51: Microphotographs of rat brain sections showing appearances of bilateral electrolytic lesions of the accumbens nuclei in 3 rat brains (a,b,c). Fig. 3b is a section from the rat brain depicted in Fig. 50. Fig. 3d shows the appearance of the tracks made following a sham lesion - the faint electrode track is seen passing through the corpus callosum on the left side.

stereotyped behaviour" could be more closely observed.

(c) Behaviour on the hole-board following an injection of 1 ml/kg saline There were no detectable differences between lesioned animals and sham-operated controls (Fig. 52, Table 32a).

(d) Behaviour on the hole-board following injection of 4 mg/kg DL-amphetamine sulphate Here again there was no detectable difference in any of the behavioural parameters between lesioned and sham-lesioned animals. This applied even to the animals with the most severe lesions (Fig. 53, Table 32b).

(e) Behaviour on the hole-board following injection of 16 mg/kg DL-amphetamine There was no detectable difference between lesioned and sham-lesioned rats. In both groups, the initial phase of "exploratory" dipping and locomotor activity stimulation rapidly gave way to a high level of "stereotyped" dipping which during the second half of the 60 minute observation period was joined and then replaced by "non-dipping stereotyped behaviour" (Fig. 54, Table 32c).

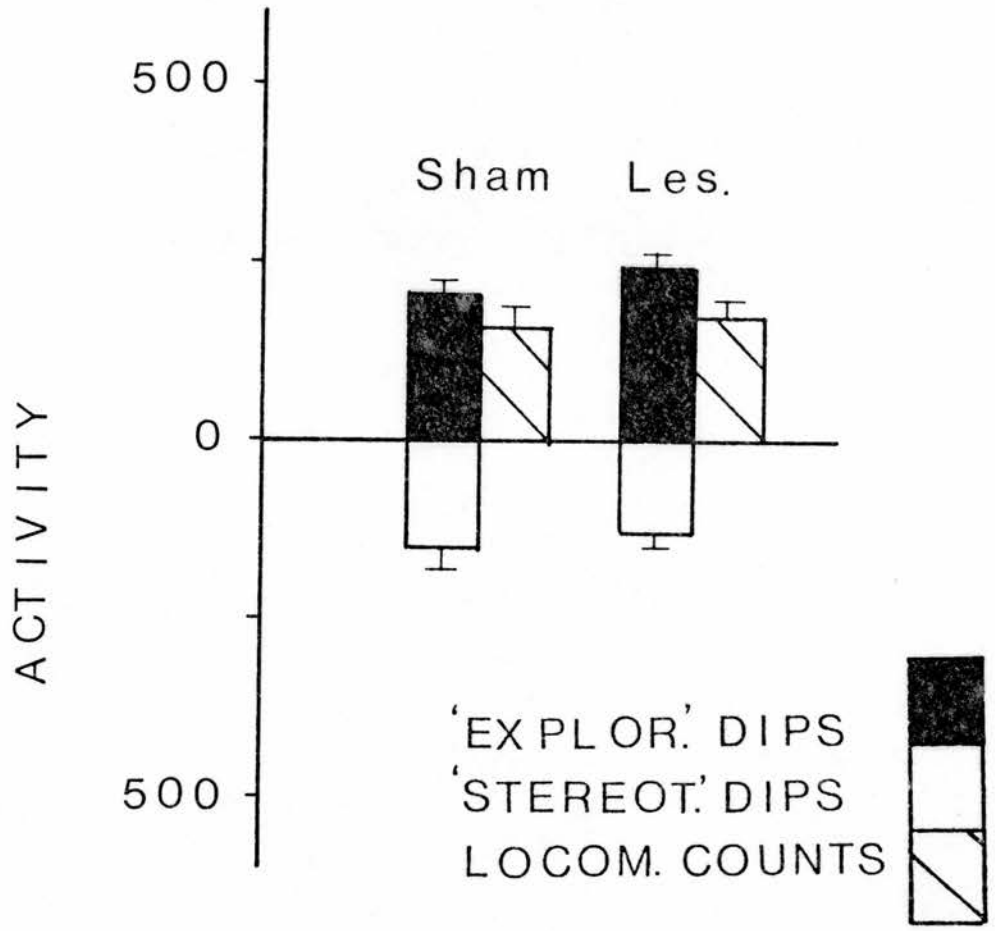


FIG. 52: Overall behavioural response in the hole-board apparatus of 6 animals with bilateral sham lesions of the accumbens nuclei ("Sham") or 10 animals with bilateral electrolytic lesions of the accumbens nuclei ("Les.") following i.p. administration of 1 ml/kg saline. Each column represents mean activity ± S.E.M. during a one-hour period immediately following the injection.

TABLE 32: Overall behavioural response in the hole-board apparatus during a one-hour observation period of animals with sham lesions of the nucleus accumbens and electrolytic lesions of the nucleus accumbens following administration to each animal at weekly intervals of (a) 1 ml/kg physiological saline, then (b) 4 mg/kg DL-amphetamine sulphate and finally (c) 16 mg/kg DL-amphetamine sulphate. Figures show mean activity during the 1 hour. Percentage damage to the nucleus is also shown (see page 70).

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

GROUP	RAT	WT	S	E	T	S/T	LOC	EXTENT OF LESIONS
Sham Lesions	1	230	95	201	296	0.32	62	
	2	240	67	186	253	0.26	84	
	3	245	116	151	267	0.43	142	
	4	250	213	287	500	0.43	191	
	5	230	256	192	448	0.57	219	
	6	225	137	220	357	0.38	245	
	MEAN ± SEM	237 ± 4	147 ± 30	206 ± 19	353 ± 41	0.40 ± 0.04	157 ± 30	
Nucleus Accumbens Lesions	1	230	25	139	164	0.15	92	50-55%
	2	215	82	144	226	0.36	91	50-75%
	3	250	113	138	351	0.32	-	60-70%
	4	220	109	266	375	0.29	280	65-75%
	5	240	127	292	419	0.30	222	50-55%
	6	200	137	173	310	0.44	103	80-85%
	7	190	149	370	519	0.29	135	55-60%
	8	225	253	407	660	0.38	199	70-75%
	9	215	160	296	456	0.35	310	75-80%
	10	240	131	206	337	0.39	136	70-80%
	Mean ± SEM	222 ± 6	129 ± 18	243 ± 31	382 ± 45	0.33 ± 0.02	174 ± 26	

TABLE 32a - Saline 1 ml/kg i.p.

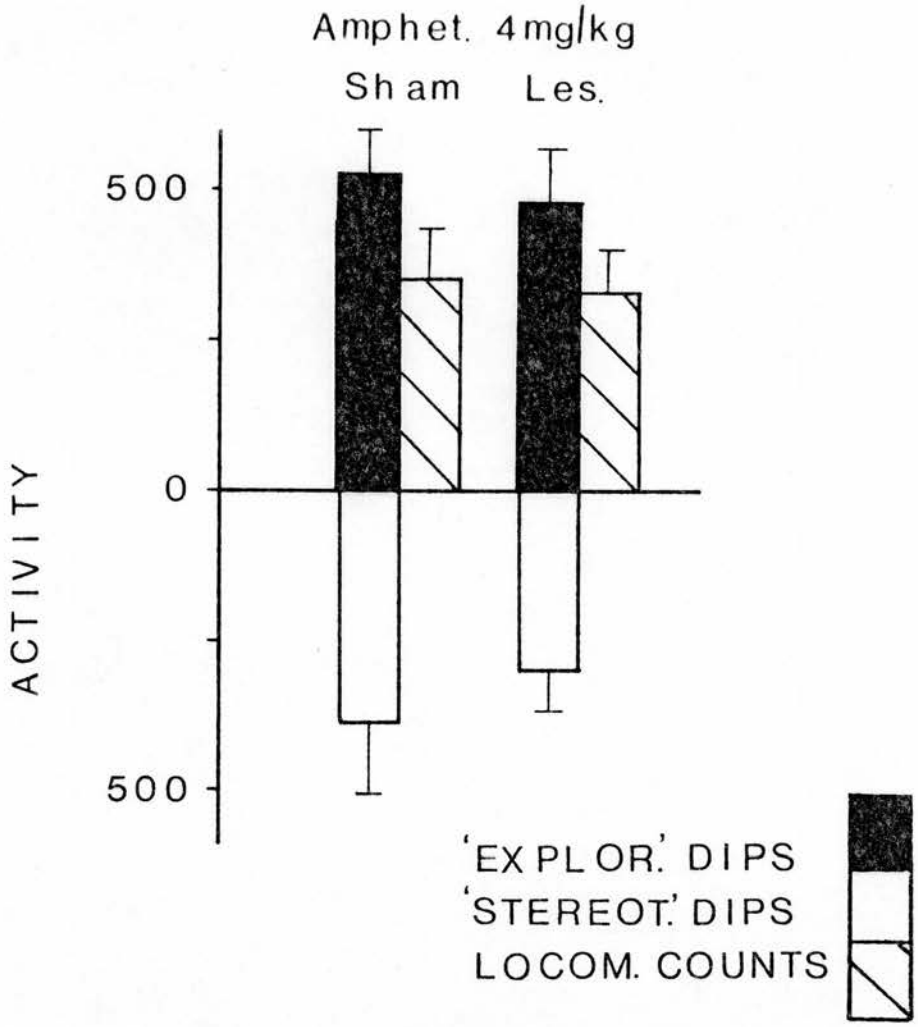


FIG. 53: Overall behavioural response in the hole-board apparatus of 6 animals with bilateral sham lesions of the accumbens nuclei ("Sham") or 10 animals with bilateral electrolytic lesions of the accumbens nuclei ("Les.") following i.p. administration of 4 mg/kg DL-amphetamine sulphate. Each column represents mean activity ± S.E.M. during a one-hour period immediately following the injection.

TABLE 32b - Amphetamine 4 mg/kg

GROUP	RAT	S	E	T	S/T	LOC
Sham Lesions	1	554	378	932	0.59	235
	2	71	564	635	0.11	295
	3	267	392	659	0.41	116
	4	297	829	1126	0.26	735
	5	256	626	882	0.29	410
	6	874	368	1242	0.70	334
	MEAN ± SEM	387 ± 116	526 ± 75	913 ± 100	0.39 ± 0.09	354 ± 86
Nucleus Accumbens Lesions	1	108	318	426	0.25	152
	2	156	232	388	0.40	192
	3	410	379	789	0.52	149
	4	296	1097	1393	0.21	436
	5	14	52	66	0.21	37
	6	844	311	1155	0.73	171
	7	416	682	1098	0.38	624
	8	139	490	629	0.22	200
	9	276	501	777	0.36	598
	10	309	719	1028	0.30	651
	MEAN ± SEM	297 ± 74	478 ± 94	775 ± 128	0.36 ± 0.05	321 ± 74

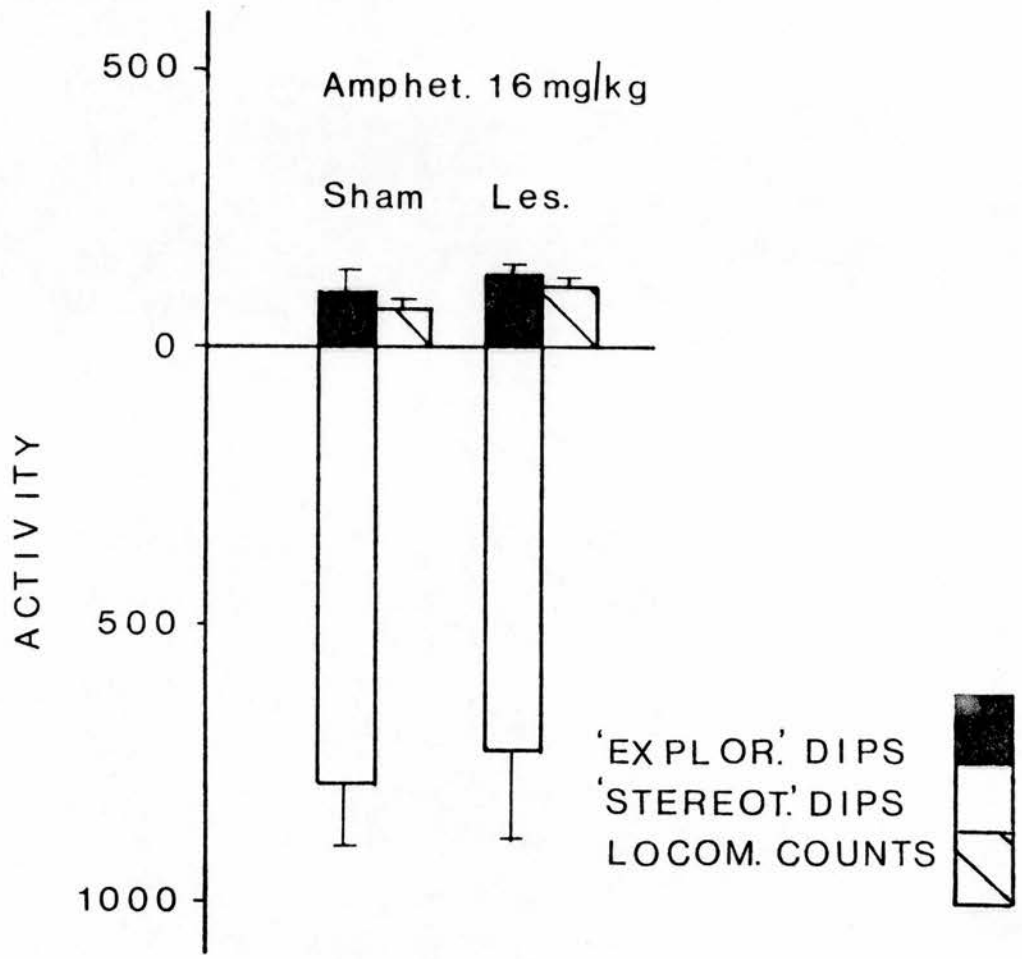


FIG. 54: Overall behavioural response in the hole-board apparatus of 6 animals with bilateral sham lesions of the accumbens nuclei ("Sham") or 10 animals with bilateral electrolytic lesions of the accumbens nuclei ("Les.") following i.p. administration of 16 mg/kg DL-amphetamine sulphate. Each column represents mean activity ± S.E.M. during a one-hour period immediately following the injection.

TABLE 32c - Amphetamine 16 mg/kg

GROUP	RAT	S	E	T	S/T	LOC
Sham Lesions	1	1082	43	1125	0.96	54
	2	386	132	518	0.75	-
	3	755	43	798	0.95	86
	4	604	286	890	0.68	124
	5	802	81	883	0.91	60
	6	1096	30	1126	0.97	20
	MEAN	787	102	890	0.87	69
	± SEM	± 112	± 39	± 93	± 0.05	± 17
Nucleus Accumbens Lesions	1	688	154	842	0.82	185
	2	1013	167	1180	0.86	165
	3	643	54	697	0.92	113
	4	859	111	970	0.89	88
	5	1852	133	1985	0.93	42
	6	350	39	389	0.90	67
	7	459	226	685	0.67	83
	8	186	99	285	0.65	159
	9	1037	64	1101	0.94	64
	10	201	225	426	0.47	158
	MEAN	729	127	856	0.80	112
	± SEM	± 158	± 21	± 157	± 0.05	± 16

C. STEREOTACTIC INJECTION OF MONOAMINE TRANSMITTERS INTO THE ACCUMBENS AND CAUDATE NUCLEI

a. Histology

After the initial experiments during which various modifications were made to stereotactic coordinates and injection technique, a high degree of accuracy was achieved in the placement of the injected material. Examples of needle tracks are shown in Figs. 55,56. Varying degrees of cortical damage were often present under the guide cannulae. This damage was presumably incurred at the time of operation but may also represent chronic irritation from the presence of the guide cannula near the cortical surface. In some animals further damage around the needle track gave the appearance of a channel of varying width in relation to the needle track, but in which the needle track could still be clearly seen.

b. Behavioural Effects

The behavioural effects of DA, NA and 5-HT injected into the two areas were studied. The monoamine solutions were made up in chilled physiological saline just before injection. These were dopamine hydrochloride, L-noradrenaline hydrochloride, and 5-hydroxytryptamine bimaleinate. 100 mg/kg nialamide was given i.p. 2 hours before the intracerebral injection.

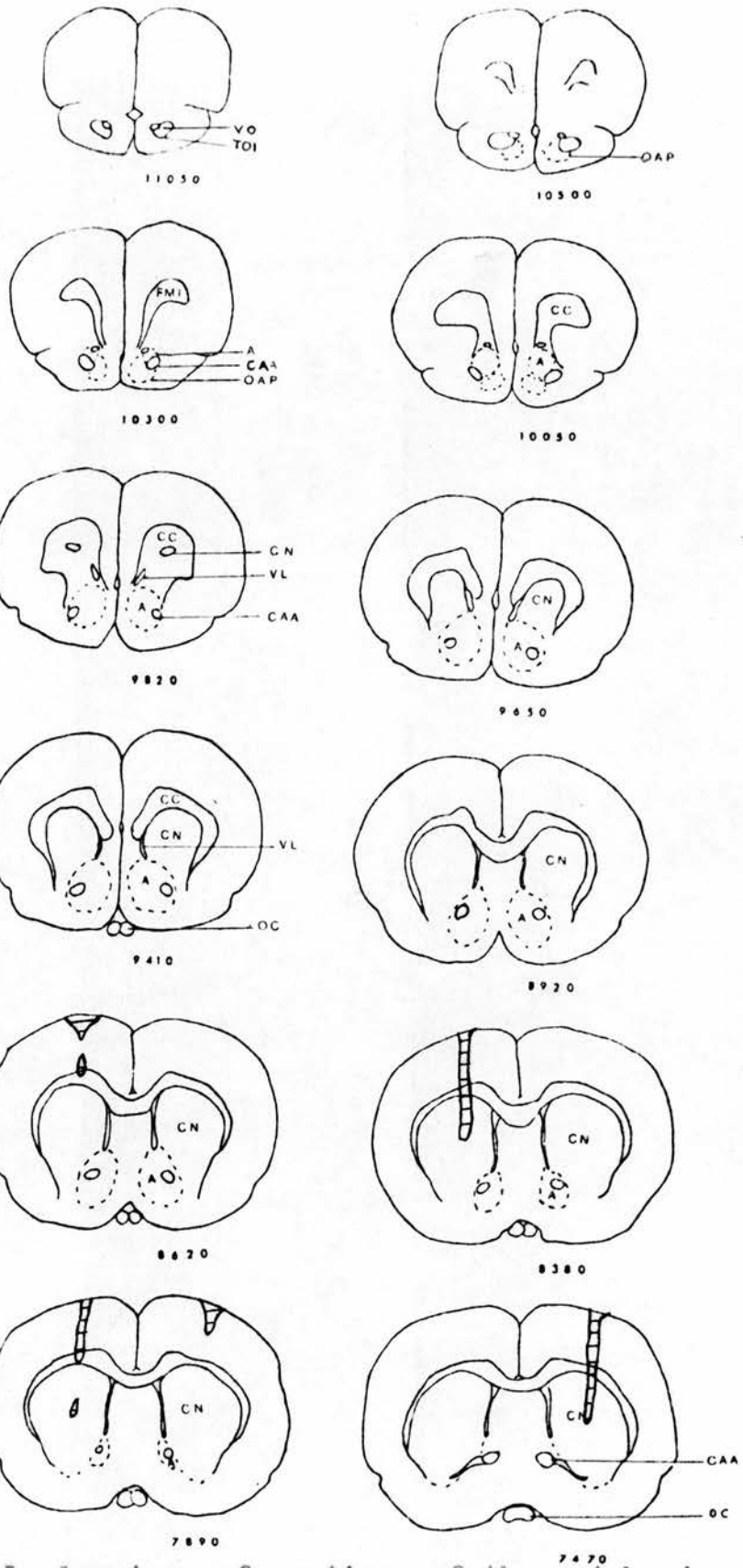


FIG. 55: Scale drawings of sections of the rat brain adapted from the Atlas of König and Klippel (1963) - see page 70. The appearance of bilateral injection tracks into the caudate-putamen nuclei at different antero-posterior coordinates is shown. These coordinates are denoted below each figure in microns in accordance with the atlas of König and Klippel. VO - olfactory ventricle; TOI - intermediate olfactory tracks; OAP - Anterior olfactory nucleus; CAA - anterior commissure; CC - corpus callosum; A - accumbens nucleus; CN - caudate-putamen; OC - optic chiasma.

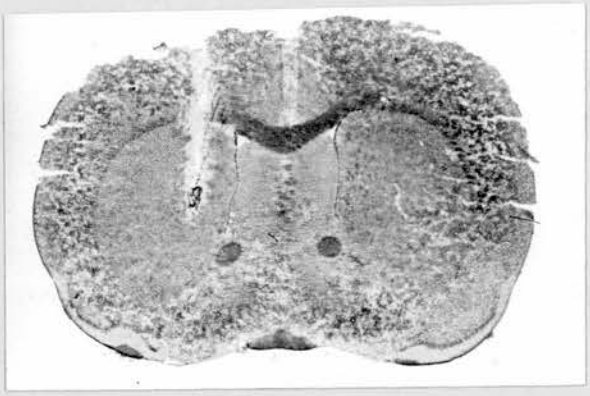
After injection in all cases there was usually a period of prostration during which the animal would lie flat on the hole-board floor, quite still. This usually wore off within a minute, but in some animals lasted as much as five minutes. Thereafter the rat would attain its normal stance, crouched over a hole, and might move around a little, dipping into a few holes. These initial effects occurred regardless of what substance, including control injections of 1 µl saline, was injected and regardless of the injected site. This initial behaviour was also not related to the degree of ease of the injection procedure. (The actual injection time was kept as constant as possible.)

(i) Response to bilateral injection of Dopamine Hydrochloride into the nucleus accumbens in Nialamide pretreated rats

Two hours after i.p. administration of 100 mg/kg nialamide, 5, 12.5, 25 or 50 µg dopamine hydrochloride contained in 1 µl physiological saline was injected bilaterally into the accumbens nuclei. Control animals were injected with 1 µl saline two hours after nialamide pretreatment.

This neurotransmitter produced a very characteristic response, with onset usually between 30 and 60 minutes and peak at 3-4 hours. The behavioural changes lasted up to 9 hours. This behaviour

a



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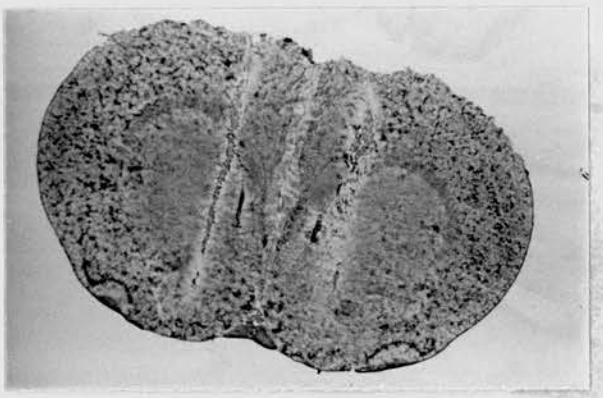

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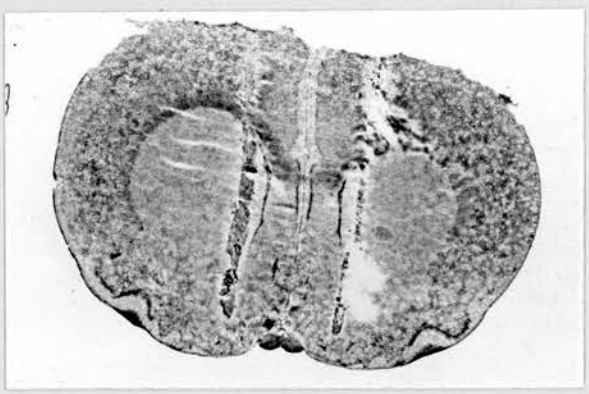

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FIG. 56: Microphotographs of rat brain sections showing appearances of needle tracks produced following bilateral injection of monoamines into the caudate-putamen nuclei (a and b) or the accumbens nuclei (c and d). Generally the actual injection point on each side did not occur at exactly the same level - see Fig. 55 which depicts serial sections of the rat brain seen in Fig. 56b.

consisted of a marked stimulation of locomotor activity and "exploratory" dipping (Figs.57,58, Tables 33,34). There was only a moderate stimulation of "stereotyped" dipping and the S/T ratio was correspondingly low. Rearing behaviour was also markedly stimulated and the animals sniffed continually at holes, floor and walls of the enclosure as they moved along. Usually the animals moved in both directions, but in a few cases they moved in one direction only i.e. clockwise or anticlockwise. This may reflect an inequality in the injection effects between the two sides. Tighter circling was never observed.

Animals injected with saline (1 µl) did not show any such response (Fig.57a). These animals spent most of the time crouched over a hole, usually in a corner, with occasional "stereotyped" dips interspersed with occasional forays during which they made a few dips.

The original three doses of dopamine employed, 12.5, 25 and 50 µg into each side, gave response levels in the same range both in intensity and duration albeit with a slight positive upward trend in response with increasing dose. It appeared that a near maximal response was achieved with a dose of 12.5 µg. An additional set of rats were therefore injected with 5 µg DA on each side. Results at this dose were extremely variable, ranging from what appeared to be a maximal response to a response little different from those of saline-treated controls.

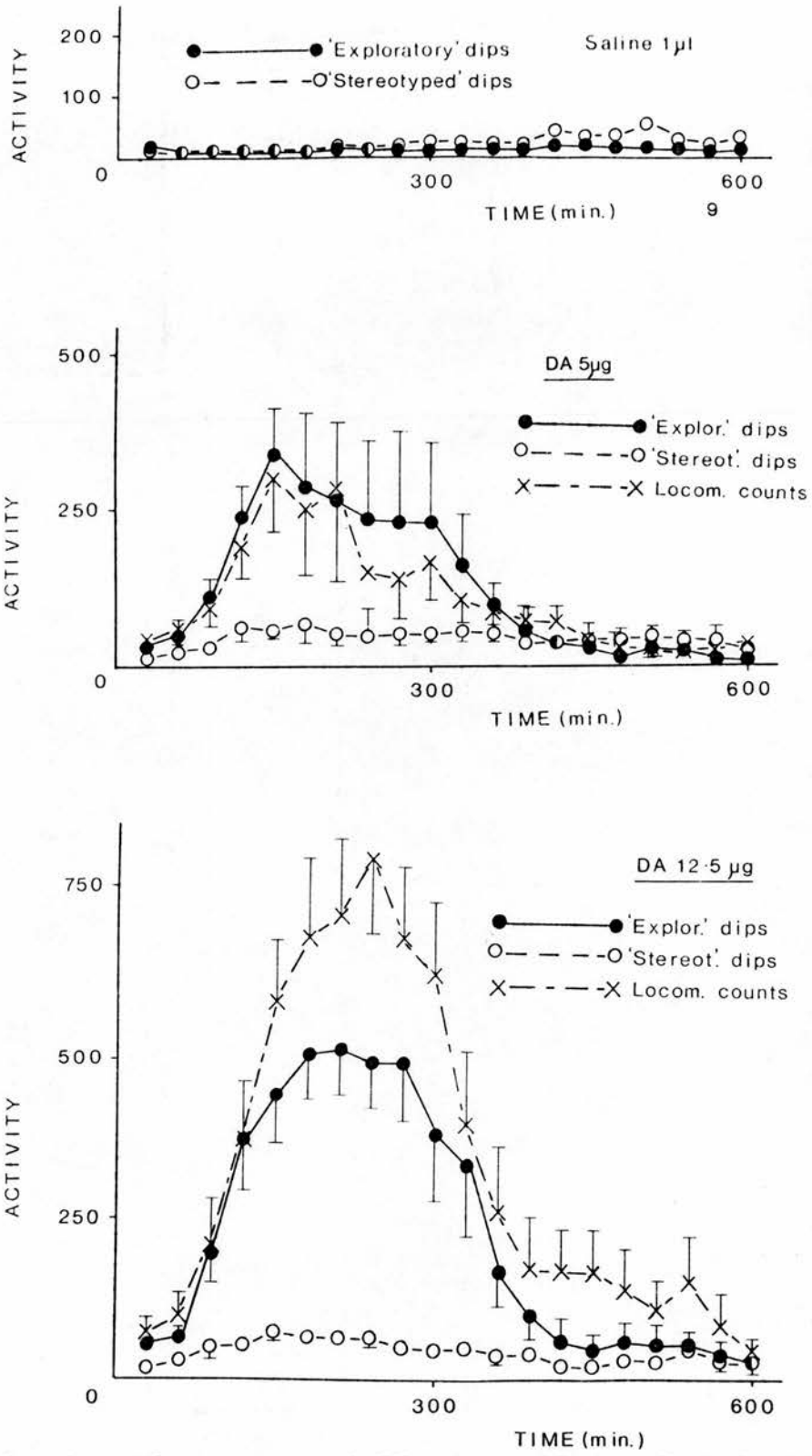

FIG. 57a: Behavioural response following bilateral injection 1 µl saline or 5 or 12.5 µg dopamine (as the hydrochloride salt) in 1 µl saline into the accumbe nuclei. The animals were pretreated with 100 mg/k i.p. nialamide 2 hours before the intracerebral injection. Each point represents mean activity ± S.E.M. of 6 or 7 rats during successive 30 min. intervals following the intracerebral injection.

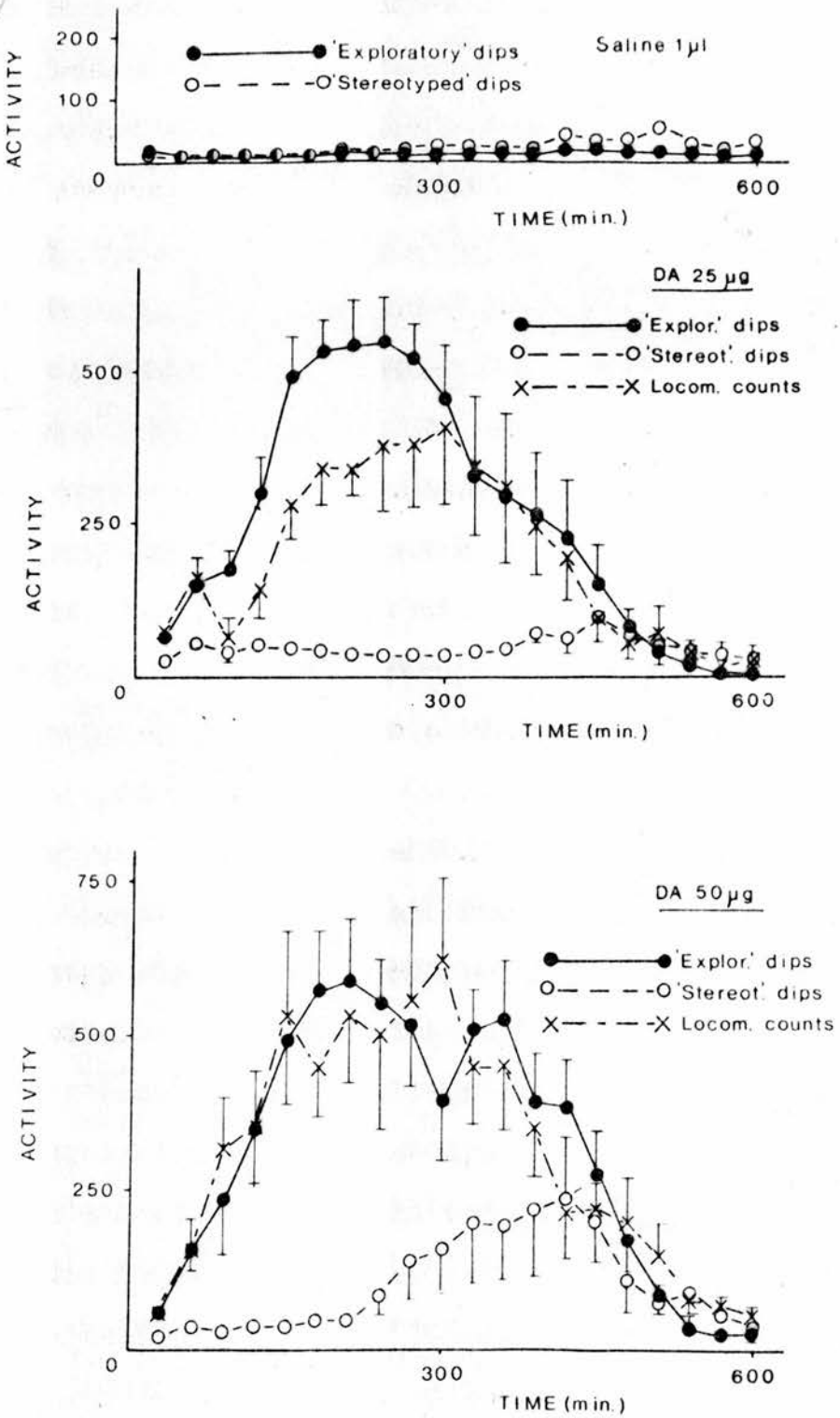

FIG. 57b: Behavioural response following bilateral injection of 1 µl saline or 25 or 50 µg dopamine (as the hydrochloride salt) in 1 µl saline into the accumbens nuclei. The animals were pretreated with 100 mg/kg i.p. nialamide 2 hours before the intracerebral injection. Each point represents mean activity ± S.E.M. of 6 or 7 rats during successive 30 min. intervals following the intracerebral injection.

TABLE 33: Behaviour in the hole-board apparatus following application of 1 µl physiological saline or 5, 12.5, 25 or 50 µg Dopamine hydrochloride in 1 µl saline to the accumbens nucleus on each side. Each animal was pretreated with Nialamide 100 mg/kg i.p. two hours before the intracerebral injection. Figures show mean activity ± S.E.M. during each successive 30 min. period following intracerebral injection of 6-7 rats.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts.

TIME INTERVAL (min)	0 - 30			30 - 60		
DOSE (µg)	S	E	LOC	S	E	LOC
0	12 ± 5	17 ± 5	42 ± 23	11 ± 7	9 ± 3	6 ± 4
5	18 ± 5	29 ± 8	37 ± 10	22 ± 8	45 ± 13	56 ± 16
12.5	14 ± 3	52 ± 15	71 ± 26	29 ± 11	66 ± 17	99 ± 40
25	11 ± 5	27 ± 13	29 ± 13	20 ± 9	61 ± 11	65 ± 34
50	20 ± 5	55 ± 18	53 ± 12	33 ± 9	156 ± 57	151 ± 28
TIME INTERVAL (min)	60 - 90			90 - 120		
DOSE (µg)	S	E	LOC	S	E	LOC
0	14 ± 10	11 ± 7	16 ± 9	12 ± 7	12 ± 7	16 ± 8
5	31 ± 9	108 ± 29	95 ± 29	60 ± 26	233 ± 54	188 ± 51
12.5	51 ± 21	194 ± 48	208 ± 67	54 ± 12	375 ± 84	372 ± 97
25	41 ± 8	175 ± 33	64 ± 32	52 ± 11	301 ± 68	139 ± 48
50	24 ± 3	237 ± 94	320 ± 89	33 ± 5	348 ± 95	358 ± 95
TIME INTERVAL (min)	120 - 150			150 - 180		
DOSE (µg)	S	E	LOC	S	E	LOC
0	13 ± 5	9 ± 5	25 ± 11	12 ± 7	7 ± 5	17 ± 9
5	55 ± 16	337 ± 84	301 ± 91	67 ± 36	285 ±123	248 ±117
12.5	75 ± 15	445 ± 79	596 ±103	66 ± 13	508 ± 76	697 ±135
25	45 ± 9	495 ± 73	279 ± 62	40 ± 10	537 ± 57	342 ± 65
50	35 ± 10	496 ±118	533 ±149	43 ± 16	575 ±102	452 ± 90

(Contd.)

TABLE 33: continued

TIME INTERVAL (min)	180 - 210			210 - 240		
DOSE (µg)	S	E	LOC	S	E	LOC
0	14 ± 5	8 ± 4	7 ± 5	16 ± 7	11 ± 5	20 ± 9
5	51 ± 23	266 ±140	282 ±103	46 ± 15	234 ±141	151 ± 66
12.5	66 ± 11	514 ± 75	730 ±132	67 ± 15	495 ± 78	818 ±129
25	33 ± 8	546 ± 81	339 ± 48	36 ± 9	551 ± 81	377 ±114
50	45 ± 12	588 ±108	535 ±124	84 ± 32	556 ± 73	507 ±175
TIME INTERVAL (min)	240 - 270			270 - 300		
DOSE (µg)	S	E	LOC	S	E	LOC
0	20 ± 12	11 ± 5	7 ± 4	25 ± 14	10 ± 5	26 ± 15
5	49 ± 25	228 ±150	141 ± 78	49 ± 16	228 ±132	165 ± 64
12.5	52 ± 10	495 ± 97	694 ±117	45 ± 11	387 ±112	634 ±126
25	37 ± 11	526 ± 60	382 ±118	35 ± 9	455 ± 93	405 ±138
50	139 ± 67	521 ±112	561 ±164	162 ± 91	494 ±107	626 ±147
TIME INTERVAL (min)	300 - 330			330 - 360		
DOSE (µg)	S	E	LOC	S	E	LOC
0	24 ± 9	10 ± 4	19 ± 11	23 ± 7	12 ± 4	16 ± 9
5	54 ± 18	161 ± 82	104 ± 33	56 ± 17	96 ± 39	91 ± 30
12.5	48 ± 12	333 ±118	400 ±114	40 ± 14	168 ± 60	264 ±105
25	39 ± 9	324 ±104	341 ±131	44 ± 12	295 ±123	312 ±131
50	197 ±107	516 ± 79	451 ±101	195 ± 93	528 ±104	453 ±117
TIME INTERVAL (min)	360 - 390			390 - 420		
DOSE (µg)	S	E	LOC	S	E	LOC
0	22 ± 7	11 ± 5	24 ± 14	46 ± 13	18 ± 4	31 ± 14
5	37 ± 9	56 ± 8	65 ± 26	33 ± 13	34 ± 15	72 ± 28
12.5	41 ± 13	99 ± 43	173 ± 87	27 ± 8	60 ± 37	168 ± 74
25	71 ± 14	266 ±110	244 ± 87	62 ± 19	225 ±102	194 ± 69
50	221 ±117	395 ± 89	357 ± 93	238 ±118	385 ± 87	216 ± 76

(Contd.)

TABLE 33: continued

TIME INTERVAL (min)	420 - 450			450 - 480		
DOSE (µg)	S	E	LOC	S	E	LOC
0	36 ± 11	19 ± 4	21 ± 9	38 ± 12	19 ± 7	21 ± 11
5	38 ± 13	27 ± 10	41 ± 24	33 ± 16	16 ± 8	36 ± 21
12.5	22 ± 8	45 ± 28	171 ± 71	32 ± 11	61 ± 33	142 ± 71
25	93 ± 37	151 ± 74	96 ± 47	66 ± 27	81 ± 37	55 ± 28
50	205 ± 73	279 ± 76	227 ± 69	118 ± 57	177 ± 55	204 ± 76
TIME INTERVAL (min)	480 - 510			510 - 540		
DOSE (µg)	S	E	LOC	S	E	LOC
0	54 ± 16	19 ± 8	22 ± 9	30 ± 5	16 ± 8	31 ± 12
5	43 ± 21	27 ± 14	32 ± 14	33 ± 17	22 ± 6	26 ± 9
12.5	31 ± 8	55 ± 35	110 ± 50	44 ± 11	57 ± 24	156 ± 79
25	47 ± 15	42 ± 20	69 ± 48	42 ± 17	18 ± 7	38 ± 15
50	75 ± 16	88 ± 21	149 ± 61	84 ± 28	34 ± 13	96 ± 33
TIME INTERVAL (min)	540 - 570			570 - 600		
DOSE (µg)	S	E	LOC	S	E	LOC
0	22 ± 8	10 ± 4	10 ± 2	35 ± 12	18 ± 11	32 ± 16
5	34 ± 27	12 ± 6	20 ± 6	27 ± 11	12 ± 3	28 ± 5
12.5	24 ± 10	36 ± 27	87 ± 58	27 ± 14	26 ± 17	38 ± 28
25	34 ± 20	8 ± 3	16 ± 13	29 ± 21	5 ± 3	20 ± 9
50	57 ± 22	24 ± 10	83 ± 19	35 ± 15	23 ± 9	48 ± 22

Details of the responses of individual rats can be found in the Appendix (Tables 34 - 38).

TABLE 34: Overall behaviour in the hole-board apparatus during a 10-hour observation period following application of 1 µl physiological saline or 5, 12.5, 25 or 50 µg dopamine hydrochloride in 1 µl saline into the nucleus accumbens on each side. Rats were pretreated with nialamide 100 mg/kg i.p. 2 hours before the intracerebral injection. Figures show overall response of each rat during the entire 10 hour period.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

DOSE (µg)	ACT-IVITY	RAT NO.							MEAN ± SEM
		1	2	3	4	5	6	7	
0	S	384	331	792	220	394	757		480 ± 96
	E	154	234	447	204	99	416		259 ± 58
	T	538	565	1239	424	493	1173		739 ± 150
	S/T	0.71	0.59	0.64	0.52	0.80	0.65		0.65 ± 0.04
	LOC	117	411	595	334	124	-		316 ± 91
5	S	2279	404	628	1220	798	305	225	837 ± 272
	E	2729	7183	2753	2558	551	685	711	2453 ± 877
	T	5008	7587	3381	3778	1349	990	936	3290 ± 929
	S/T	0.46	0.05	0.18	0.32	0.59	0.31	0.24	0.31 ± 0.07
	LOC	3256	3818	3599	1359	923	756	1069	2111 ± 520
12.5	S	1195	1022	707	266	999	840	949	854 ± 114
	E	6114	6620	3769	3383	6110	1327	3900	4460 ± 722
	T	7309	7642	4476	3649	7109	2167	4849	5314 ± 790
	S/T	0.16	0.13	0.16	0.07	0.14	0.39	0.20	0.18 ± 0.04
	LOC	13524	9225	5412	5947	5632	2633	3513	6545 ± 1404
25	S	814	320	693	1031	732	1678		878 ± 185
	E	3344	2999	3745	6581	6002	7862		5089 ± 816
	T	4158	3319	4438	7612	6734	9540		5967 ± 978
	S/T	0.20	0.10	0.16	0.14	0.11	0.18		0.15 ± 0.02
	LOC	4239	1043	965	8407	-	3587		3648 ± 1360
50	S	1421	2597	989	400	1467	5422		2049 ± 736
	E	7882	7435	6369	5968	6990	4212		6476 ± 535
	T	9303	10032	7358	6368	8457	9635		8526 ± 581
	S/T	0.15	0.26	0.13	0.06	0.17	0.56		0.22 ± 0.07
	LOC	-	6083	-	5757	1959	4929		4682 ± 910

Kruskal-Wallis one-way analysis of variance: $p < 0.001$ for "exploratory" dips, < 0.01 for S/T ratio and locomotor counts.

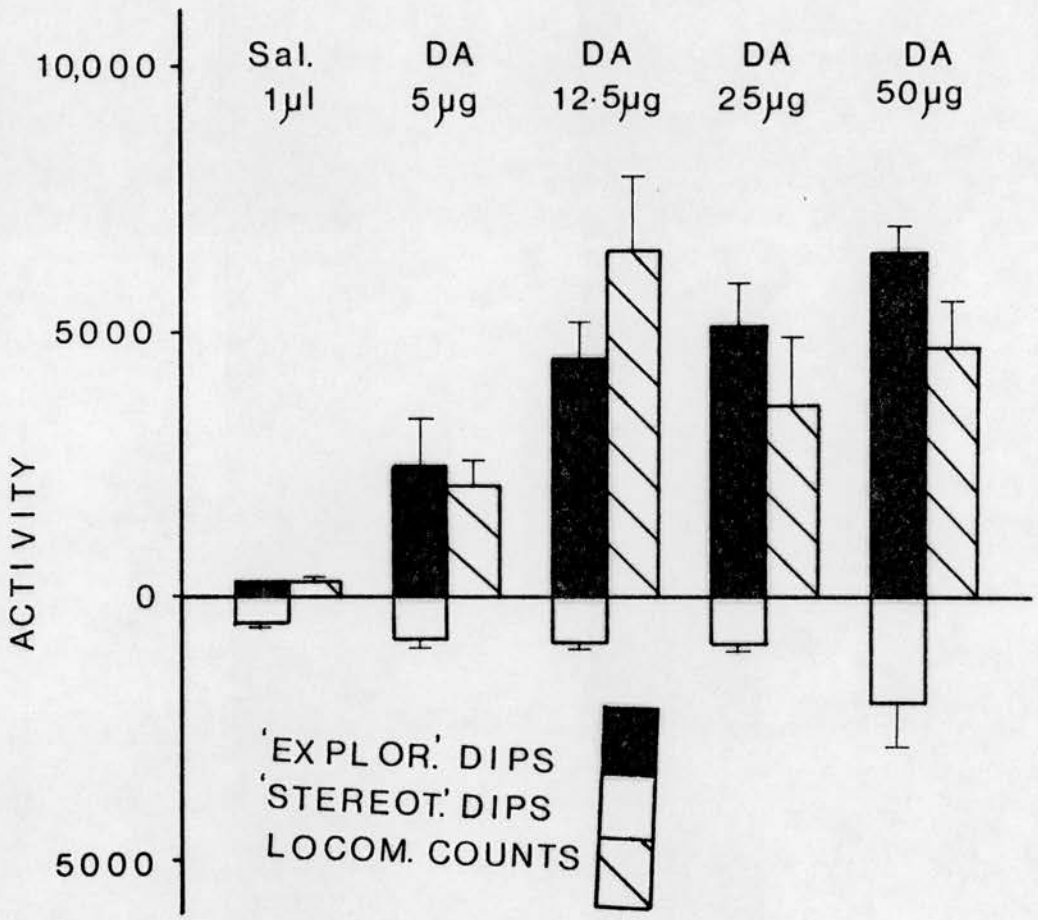

FIG. 58: Overall behavioural response in the hole-board apparatus following bilateral injection of 1 µl saline or 5, 12.5, 25 or 50 µg dopamine (as the hydrochloride salt) into the accumbens nuclei. Each column represents overall mean activity ± S.E.M. of 6 or 7 rats during the 10 hour period immediately following the intracerebral injection. Each animal was pretreated with 100 mg/kg nialamide i.p. 2 hours before the intracerebral injection.

A Kruskal-Wallis one-way analysis of variance comparing the overall response during the 10 hour observation period in all five groups of rats showed that the behavioural differences between the different doses of DA and of saline were statistically significant($p < 0.001$ for "exploratory" dips, < 0.01 for locomotor counts and < 0.01 for S/T ratio, not significant for stereotyped dips.) It should be noted that locomotor counts were subject to great variation. The maximal locomotor response appears to have occurred with a dose of 12.5 µg DA.

(ii) Response to bilateral injection of dopamine hydrochloride into the caudate nucleus in Nialamide pretreated rats

Two hours after administration of 100 mg/kg nialamide, 12.5, 25, 50 µg dopamine hydrochloride contained in 1 µl physiological saline was injected bilaterally into the caudate nucleus. Control animals were injected with 1 µl saline two hours after nialamide pretreatment.

A very different pattern of response was obtained in comparison with that following the n.accumbens injections. The behavioural response had its onset at 30 - 60 min. and peak at 5 hours. The response thereafter lasted up to 10 hours. In contrast to the response to DA injection into the accumbens nuclei, the injection into the caudate nuclei resulted in a marked dose-related stimulation of "stereotyped" dipping. "Exploratory" dipping and

locomotor activity were also stimulated moderately, but "stereotyped" dipping was predominant (Figs.59, 60, Tables 35,36). The S/T ratio therefore remained very high. Not much sniffing behaviour was noted.

At the highest dose of DA employed, "non-dipping stereotyped" behaviour (see page 146) was also evident usually between 4 and 6 hours after injection. A Kruskal-Wallis one-way analysis of variance showed that the differences between the responses over the entire 10 hour period of the record to saline and the three doses of DA employed (12.5, 25 and 50 µg) were statistically significant ($p < 0.001$) for "stereotyped" dips but not for the S/T ratio. The differences in "exploratory" dipping were also significant ($p < 0.001$) but changes in locomotor counts were not. Because the S/T ratios for saline-treated controls were relatively high and the DA administration increased this only slightly, the changes in S/T ratio were also not significant.

(iii) <u>Effect of pretreatment with haloperidol on the response to bilateral injection of 25 µg dopamine hydrochloride into the accumbens and caudate nuclei in nialamide pretreated rats</u>

Animals were pretreated with nialamide 100 mg/kg i.p. Ninety min. later they were further treated with 0.4 mg/kg haloperidol or 0.8 mg/kg haloperidol i.p. A further 30 minutes later 25 µg DA was injected bilaterally into the accumbens or caudate nuclei and the animals studied on the hole-board for three hours.

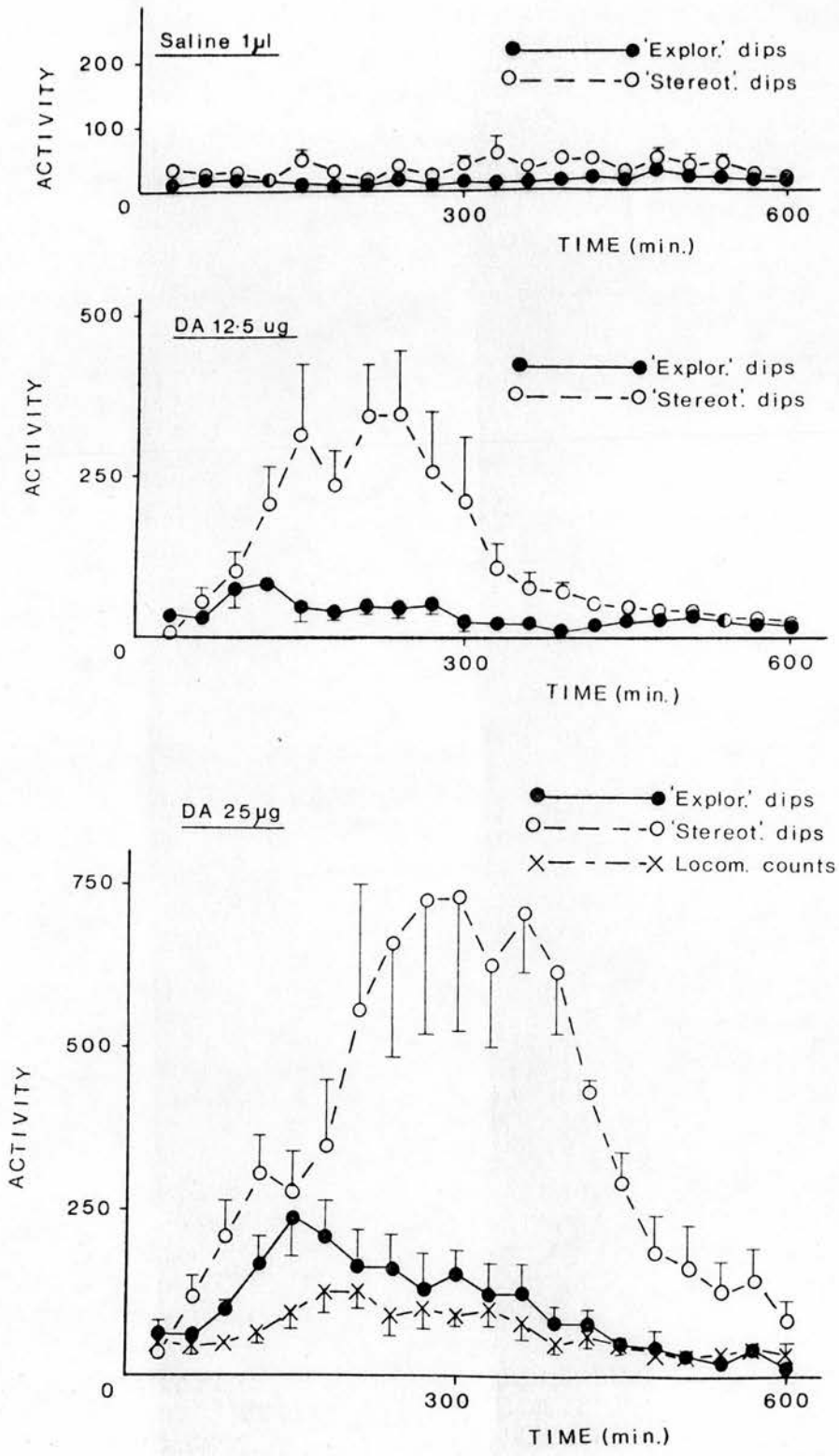

FIG. 59a: Behavioural response in the hole-board apparatus following bilateral injection of 1 µl saline or 12.5 or 25 µg dopamine (as the hydrochloride sal in 1 µl saline into the caudate-putamen nucleus. Each point represents the mean activity ± S.E.M. of 6 or 7 rats during successive 30 min. interval following the intracerebral injection. Animals were pretreated with 100 mg/kg nialamide i.p. 2 hours before the intracerebral injection.

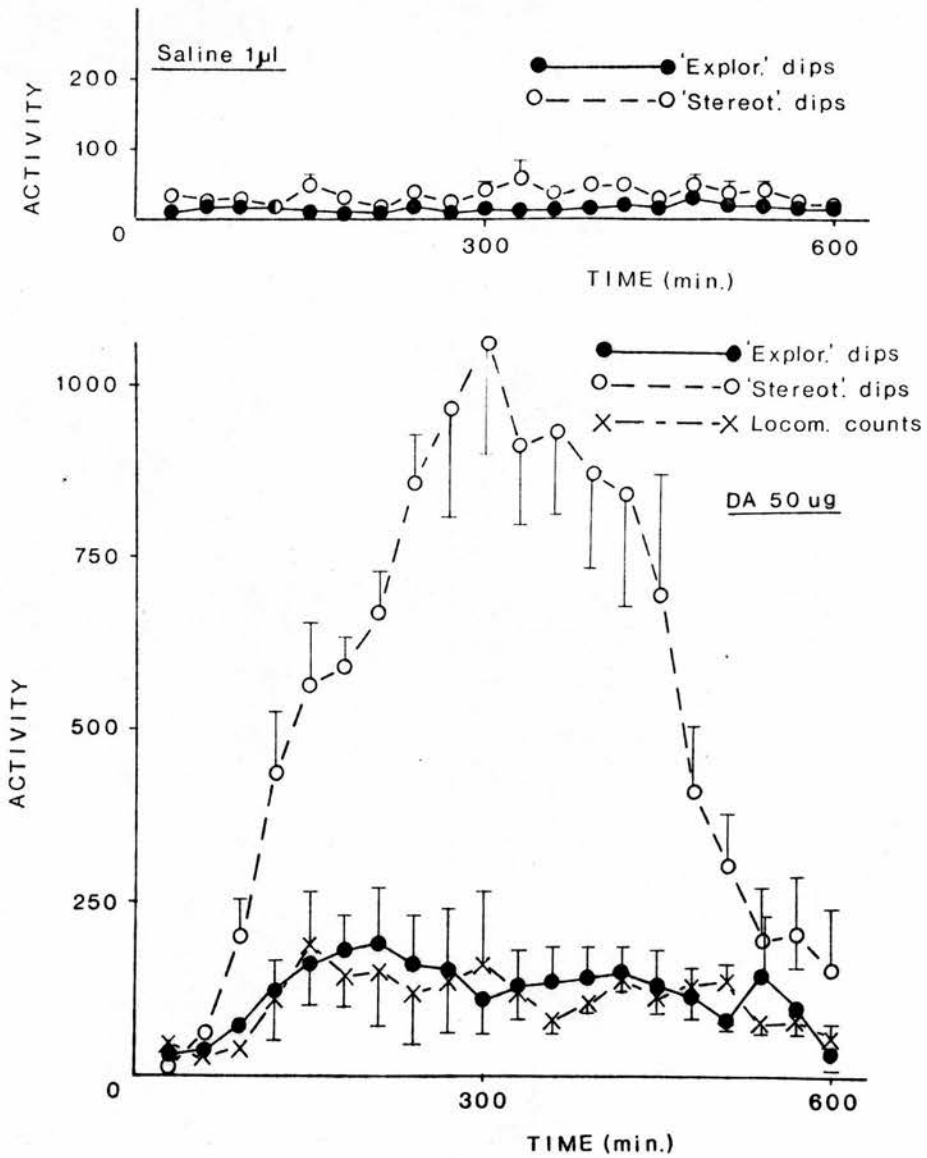

FIG. 59b: Behavioural response in the hole-board apparatus following bilateral injection of 1 µl saline or 50 µg dopamine (as the hydrochloride salt) in 1 µl saline into the caudate-putamen nucleus. Each point represents the mean activity ± S.E.M. of 6 or 7 rats during successive 30 min. intervals following the intracerebral injection. Animals were pretreated with 100 mg/kg nialamide i.p. 2 hours before the intracerebral injection.

TABLE 35: Behaviour in the hole-board apparatus following application of 1 µl physiological saline or 12.5, 25 or 50 µg dopamine hydrochloride in 1 µl saline to the caudate nucleus on each side. Each animal was pretreated with Nialamide 100 mg/kg i.p. two hours before the intracerebral injection. Figures show mean activity ± S.E.M. during each successive 30 min. period following intracerebral injection of 6 rats.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts.

TIME INTERVAL (min)	0 - 30			30 - 60		
DOSE (µg)	S	E	LOC	S	E	LOC
0	11 ± 4	34 ± 10	46 ± 9	27 ± 10	18 ± 7	5 ± 4
12.5	12 ± 4	30 ± 134	42 ± 11	64 ± 22	31 ± 11	18 ± 6
25	34 ± 8	58 ± 20	51 ± 12	121 ± 34	62 ± 15	43 ± 14
50	17 ± 2	29 ± 7	45 ± 11	61 ± 11	37 ± 9	32 ± 8
TIME INTERVAL (min)	60 - 90			90 - 120		
DOSE (µg)	S	E	LOC	S	E	LOC
0	29 ± 7	15 ± 5	21 ± 16	21 ± 4	13 ± 4	12 ± 5
12.5	101 ± 32	74 ± 33	49 ± 19	206 ± 68	82 ± 33	79 ± 37
25	207 ± 60	100 ± 11	51 ± 14	304 ± 65	168 ± 37	65 ± 15
50	202 ± 58	71 ± 16	38 ± 9	439 ± 92	119 ± 49	115 ± 70
TIME INTERVAL (min)	120 - 150			150 - 180		
DOSE (µg)	S	E	LOC	S	E	LOC
0	50 ± 17	10 ± 3	13 ± 6	31 ± 10	7 ± 4	13 ± 5
12.5	314 ± 131	47 ± 19	52 ± 18	237 ± 61	41 ± 15	66 ± 23
25	352 ± 111	210 ± 58	129 ± 39	562 ± 214	167 ± 58	130 ± 34
50	565 ± 97	159 ± 64	192 ± 84	590 ± 49	179 ± 57	145 ± 54

(Contd.)

TABLE 35: continued

TIME INTERVAL (min)	180 - 210			210 - 240		
DOSE (µg)	S	E	LOC	S	E	LOC
0	14 ± 3	5 ± 2	9 ± 7	41 ± 14	18 ± 9	21 ± 17
12.5	346 ± 89	49 ± 17	48 ± 24	346 ±108	43 ± 14	55 ± 18
25	562 ±215	167 ± 58	130 ± 34	657 ±201	159 ± 59	91 ± 29
50	671 ± 66	190 ± 88	151 ± 88	858 ± 80	160 ± 77	121 ± 82
TIME INTERVAL (min)	240 - 270			270 - 300		
DOSE (µg)	S	E	LOC	S	E	LOC
0	24 ± 5	8 ± 3	8 ± 4	47 ± 12	13 ± 5	13 ± 7
12.5	254 ±103	48 ± 18	45 ± 12	208 ±107	26 ± 15	27 ± 12
25	726 ±225	135 ± 55	101 ± 34	728 ±226	154 ± 36	96 ± 24
50	971 ±174	152 ± 95	133 ± 80	1075 ±184	110 ± 58	155 ±119
TIME INTERVAL (min)	300 - 330			330 - 360		
DOSE (µg)	S	E	LOC	S	E	LOC
0	58 ± 26	12 ± 4	13 ± 9	36 ± 13	16 ± 5	12 ± 5
12.5	110 ± 36	22 ± 6	61 ± 19	77 ± 27	18 ± 5	41 ± 15
25	625 ±139	124 ± 49	99 ± 25	703 ± 99	127 ± 48	82 ± 28
50	917 ±126	126 ± 57	118 ± 46	939 ±133	134 ± 55	78 ± 23
TIME INTERVAL (min)	360 - 390			390 - 420		
DOSE (µg)	S	E	LOC	S	E	LOC
0	51 ± 13	16 ± 6	12 ± 7	50 ± 10	20 ± 5	18 ± 10
12.5	71 ± 14	12 ± 4	18 ± 6	51 ± 14	20 ± 6	31 ± 13
25	617 ±106	80 ± 30	51 ± 14	429 ± 22	79 ± 24	61 ± 16
50	872 ±160	139 ± 50	107 ± 14	846 ±181	146 ± 43	138 ± 19

(Contd.)

TABLE 35: continued

TIME INTERVAL (min)	420 - 450			450 - 480		
DOSE (µg)	S	E	LOC	S	E	LOC
0	32 ± 13	14 ± 4	16 ± 6	48 ± 15	31 ± 9	28 ± 13
12.5	42 ± 6	25 ± 5	44 ± 10	39 ± 8	24 ± 6	34 ± 11
25	295 ± 50	52 ± 16	53 ± 15	188 ± 62	46 ± 28	34 ± 13
50	698 ±194	129 ± 57	116 ± 28	416 ±104	113 ± 32	127 ± 33
TIME INTERVAL (min)	480 - 510			510 - 540		
DOSE (µg)	S	E	LOC	S	E	LOC
0	41 ± 16	22 ± 7	35 ± 14	47 ± 11	20 ± 7	37 ± 17
12.5	41 ± 6	25 ± 4	34 ± 7	26 ± 5	15 ± 5	20 ± 8
25	164 ± 70	30 ± 9	30 ± 6	130 ± 47	24 ± 10	35 ± 10
50	306 ± 84	79 ± 19	134 ± 25	195 ± 83	144 ± 94	82 ± 34
TIME INTERVAL (min)	540 - 570			570 - 600		
DOSE (µg)	S	E	LOC	S	E	LOC
0	27 ± 12	16 ± 5	17 ± 6	19 ± 9	9 ± 5	10 ± 7
12.5	25 ± 5	14 ± 4	33 ± 10	20 ± 6	15 ± 4	37 ± 11
25	152 ± 49	37 ± 6	40 ± 13	86 ± 35	17 ± 8	34 ± 15
50	205 ± 91	101 ± 59	82 ± 23	148 ± 96	38 ± 19	53 ± 24

Details of the responses of individual rats can be found in the Appendix (Tables 39 - 43).

TABLE 36: Overall behavioural response in the hole-board apparatus during a 10 hour observation period following injection of 1 µl physiological saline or 12.5, 25 or 50 ug dopamine hydrochloride in 1 µl saline into the caudate nucleus on each side. Animals were pretreated with nialamide 100 mg/kg two hours before the intracerebral injection. Figures show overall response of each rat during the 10 hour period.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

DOSE (µg)	ACT-IVITY	RAT NO. 1	2	3	4	5	6	7	MEAN ± SEM
0	S	543	832	394	1249	494	732		707 ± 126
	E	369	66	133	327	440	561		316 ± 77
	T	912	898	527	1576	934	1293		1023 ± 148
	S/T	0.60	0.93	0.75	0.79	0.53	0.57		0.69 ± 0.06
	LOC	352	22	99	-	424	752		330 ± 130
12.5	S	4093	4706	1401	3874	1793	961	1317	2592 ± 603
	E	888	1424	478	443	432	542	337	649 ± 145
	T	4981	6130	1879	4317	2225	1503	1654	3241 ± 705
	S/T	0.82	0.77	0.75	0.90	0.81	0.64	0.80	0.78 ± 0.03
	LOC	-	808	757	717	934	665	182	677 ± 105
25	S	5229	4930	11696	5832	6054	10415		7359 ± 1192
	E	4489	2025	1597	1250	1713	1413		2081 ± 494
	T	9718	6955	13293	7082	7767	11828		9440 ± 1082
	S/T	0.54	0.71	0.88	0.82	0.78	0.88		0.77 ± 0.05
	LOC	1462	2668	454	1622	1294	1297		1466 ± 291
50	S	6932	9262	16294	10711	8073	13965		10873 ± 1471
	E	1686	3391	1473	2345	4443	972		2385 ± 536
	T	8618	12653	17767	13056	12516	14937		13258 ± 1233
	S/T	0.80	0.73	0.92	0.82	0.65	0.93		0.81 ± 0.04
	LOC	2379	-	1498	1164	6567	1485		2619 ± 1002

Kruskal-Wallis one-way analysis of variance: $p < 0.001$ for "stereotyped" dips and "exploratory" dips.

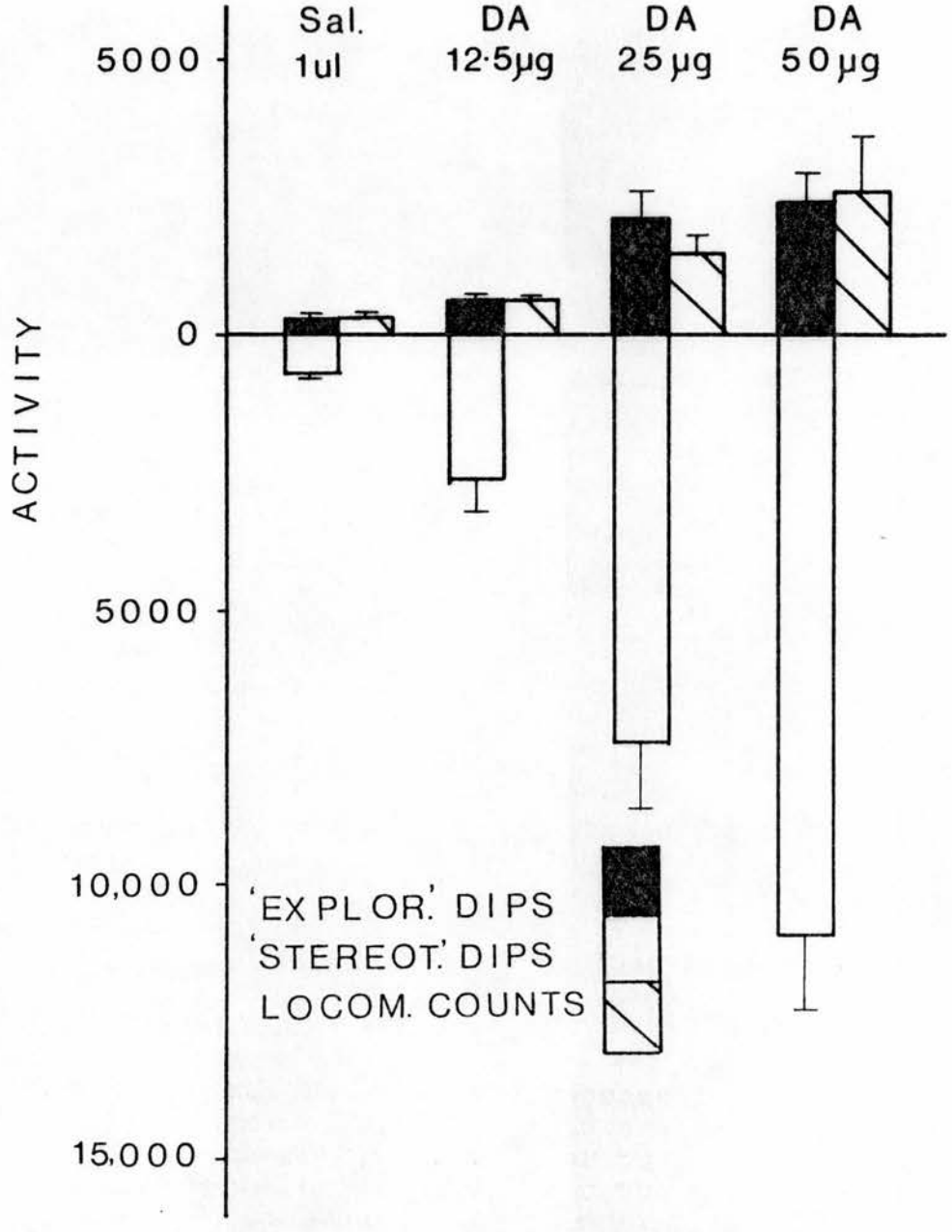

FIG. 60: Overall behavioural response in the hole-board apparatus following bilateral injection of 1 µl saline or 12.5, 25 or 50 µg dopamine (as the hydrochloride salt) into the caudate-putamen nuclei. Each column represents overall mean activity ± S.E.M. of 6 or 7 rats during the 10 hour period immediately following the intracerebral injection. Each animal was pretreated with 100 mg/kg nialamide i.p. 2 hours before the intracerebral injection.

The results were compared with those from injection of DA into rats pretreated with nialamide only (see previous two sections).

Pretreatment with 0.4 mg/kg haloperidol i.p. completely blocked the response to 25 µg DA injected bilaterally into the accumbens nuclei over a three hour observation period (Fig.61, Table 37) (Mann-Whitney U-test, $p = 0.002$ for exploratory dips $p = 0.002$ for stereotyped dips, $p = 0.008$ for locomotor counts.)

0.4 mg/kg haloperidol did not invariably block the stereotyped dipping response to DA injection into the caudate nuclei but appeared to block the response in some animals and not in others in all-or-none fashion (Fig.62,Table 38). However, a dose of 0.8 mg/kg haloperidol virtually abolished the response (Kruskal-Wallis one-way analysis of variance of results for controls, 0.4 and 0.8 mg/kg haloperidol $p < 0.01$ for "stereotyped" dips < 0.01 for exploratory dips, < 0.02 for locomotor counts.)

(iv) <u>Response to 50 µg L-noradrenaline hydrochloride injected bilaterally into the nucleus accumbens in nialamide pretreated rats</u>

50 µg L-noradrenaline hydrochloride was injected into the nucleus accumbens on each side two hours after pretreatment with 100 mg/kg nialamide i.p. and the behaviour studied on the hole-board for 10 hours.

TABLE 37: Effect of pretreatment with 0.4 mg/kg haloperidol i.p. 30 min. before the DA application on the response to 25 µg dopamine hydrochloride injected into the accumbens nucleus on each side in nialamide pretreated rats. Figures show the overall response of each rat during a 3 hour period after intracerebral injection.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

HALOPERIDOL DOSE (mg/kg)	ACT-IVITY	RAT NO. 1	2	3	4	5	6	7	MEAN ± SEM
0	S	178	114	159	327	192	288		210 ± 33
	E	890	1122	1644	1729	2311	1881		1596 ± 211
	T	1068	1236	1803	2056	2503	2169		1805 ± 228
	S/T	0.17	0.09	0.09	0.16	0.08	0.13		0.12 ± 0.01
	LOC	1062	333	478	1661	-	694		846 ± 238
0.4	S	76	7	2	17	7	9	95	** 30 ± 14
	E	463	5	7	50	7	25	140	** 100 ± 62
	T	539	12	9	67	14	34	245	131 ± 75
	S/T	0.14	0.58	0.22	0.25	0.50	0.26	0.39	0.33 ± 0.06
	LOC	894	120	14	59	66	34	244	* 238 ± 125

** p = 0.002

* p = 0.008

(Mann-Whitney U test)

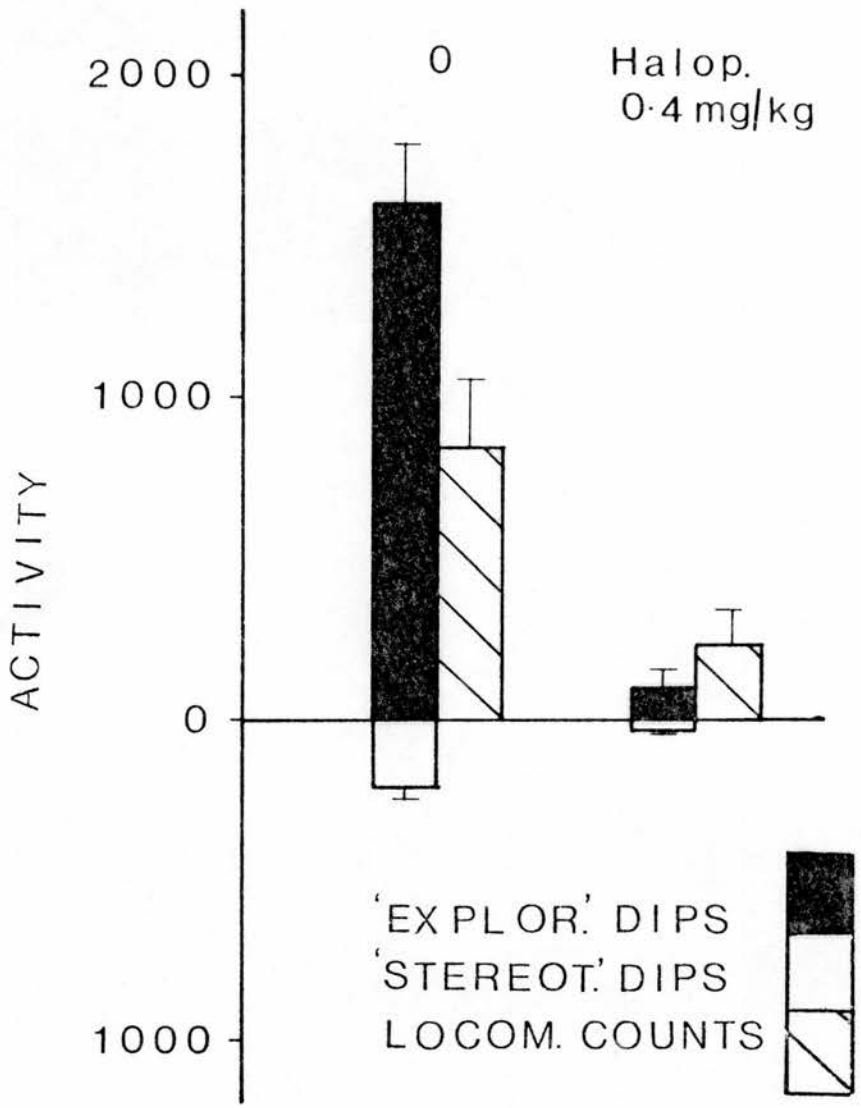

FIG. 61: Effect of i.p. pretreatment with 0.4 mg/kg haloperidol (30 min. before) on the response to bilateral injection of 25 µg dopamine (as the hydrochloride salt) in 1 µl saline. Animals were also pretreated with 100 mg/kg nialamide i.p. 2 hours before the intracerebral injection. The results after pretreatment with haloperidol are compared with those from control animals which did not receive any haloperidol (dose 0). Each column represents mean overall activity ± S.E.M. of 6 or 7 rats during the 3 hour period immediately after the intracerebral injection.

TABLE 38: Effect of pretreatment with 0.4 or 0.8 mg/kg haloperidol i.p. 30 min. before the DA application on the response to 25 ug dopamine hydrochloride injected into the caudate nucleus on each side in nialamide pretreated rats. Figures show the overall response of each rat during a 3 hour period following the intracerebral injection.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

HALOPERIDOL DOSE (mg/kg)	ACTIVITY	RAT NO.						MEAN ± SEM
		1	2	3	4	5	6	
0	S	386	1035	1356	1172	1165	2661	1296 ± 305
	E	1382	822	1064	571	646	560	841 ± 134
	T	1768	1857	2420	1743	1811	3221	2137 ± 240
	S/T	0.22	0.56	0.56	0.67	0.64	0.83	0.58 ± 0.08
	LOC	157	1787	574	541	144	510	619 ± 246
0.4	S	1065	346	28	64	1146		530 ± 241
	E	518	654	48	63	201		297 ± 123
	T	1583	1000	76	127	1347		827 ± 311
	S/T	0.67	0.35	0.37	0.50	0.85		0.55 ± 0.09
	LOC	243	830	193	68	237		314 ± 133
0.8	S	4	13	16	39	14		17 ± 6
	E	11	6	30	6	8		12 ± 5
	T	15	19	46	45	22		29 ± 7
	S/T	0.26	0.68	0.34	0.86	0.64		0.56 ± 0.11
	LOC	5	37	-	11	14		17 ± 7

Kruskal-Wallis one-way analysis of variance: $p < 0.01$ for "stereotyped" dips and "Exploratory" dips, < 0.02 for locomotor counts.

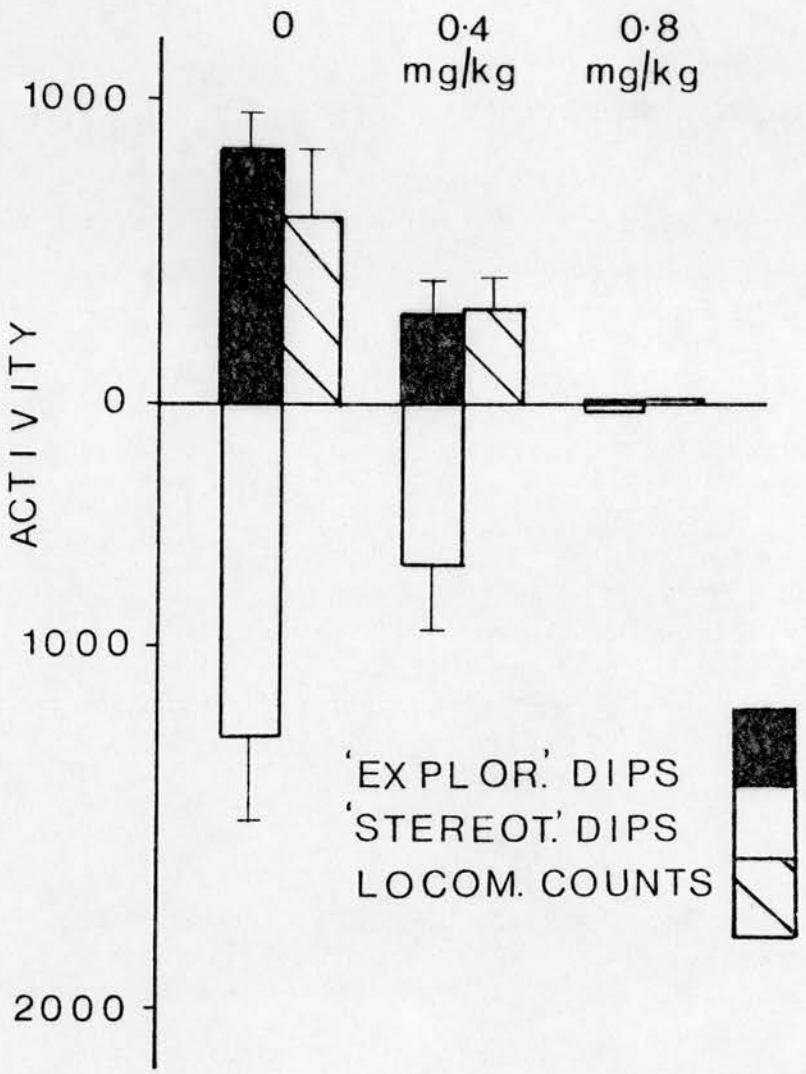

FIG. 62: Effect of i.p. pretreatment with 0.4 or 0.8 mg/kg haloperidol on the response to bilateral injection of 25 µg dopamine (as the hydrochloride salt) into the caudate-putamen nuclei. The results are compared with those from animals which did not receive haloperidol pretreatment (dose 0). All animals were pretreated with nialamide 100 mg/kg i.p. Each column represents mean overall response ± S.E.M. of 5 or 6 animals during the 3 hour period immediately following the intracerebral injection.

Noradrenaline caused a slight increase in exploratory dipping and locomotor counts when injected into the accumbens nuclei (Fig.63b,64, Tables 39,40). These changes were not statistically significant. The animals appeared no different from those that had been given saline on visual observation.

(v) Response to 50 µg L-noradrenaline hydrochloride injected bilaterally into the caudate nuclei in nialamide pretreated rats

50 µg L-noradrenaline hydrochloride was injected into the caudate nucleus on each side two hours after pretreatment with 100 mg/kg nialamide i.p. and the behaviour studied on the hole-board for 10 hours.

Noradrenaline injected into the caudate nuclei produced a moderate stimulation of "stereotyped" dipping with no effect on "exploratory" dipping or locomotor counts when compared with the responses of saline-injected controls (Figs. 65b,66, Tables 41,42). In comparison with the response of DA-injected rats, the onset of the "stereotyped" dipping response to NA was much delayed since it occurred only after 2-3 hours; the peak response was also much delayed. The intensity of the "stereotyped" dipping showed much variation between animals. The increase in the "stereotyped" dipping response was significant when compared with that of saline-treated controls ($p = 0.014$).

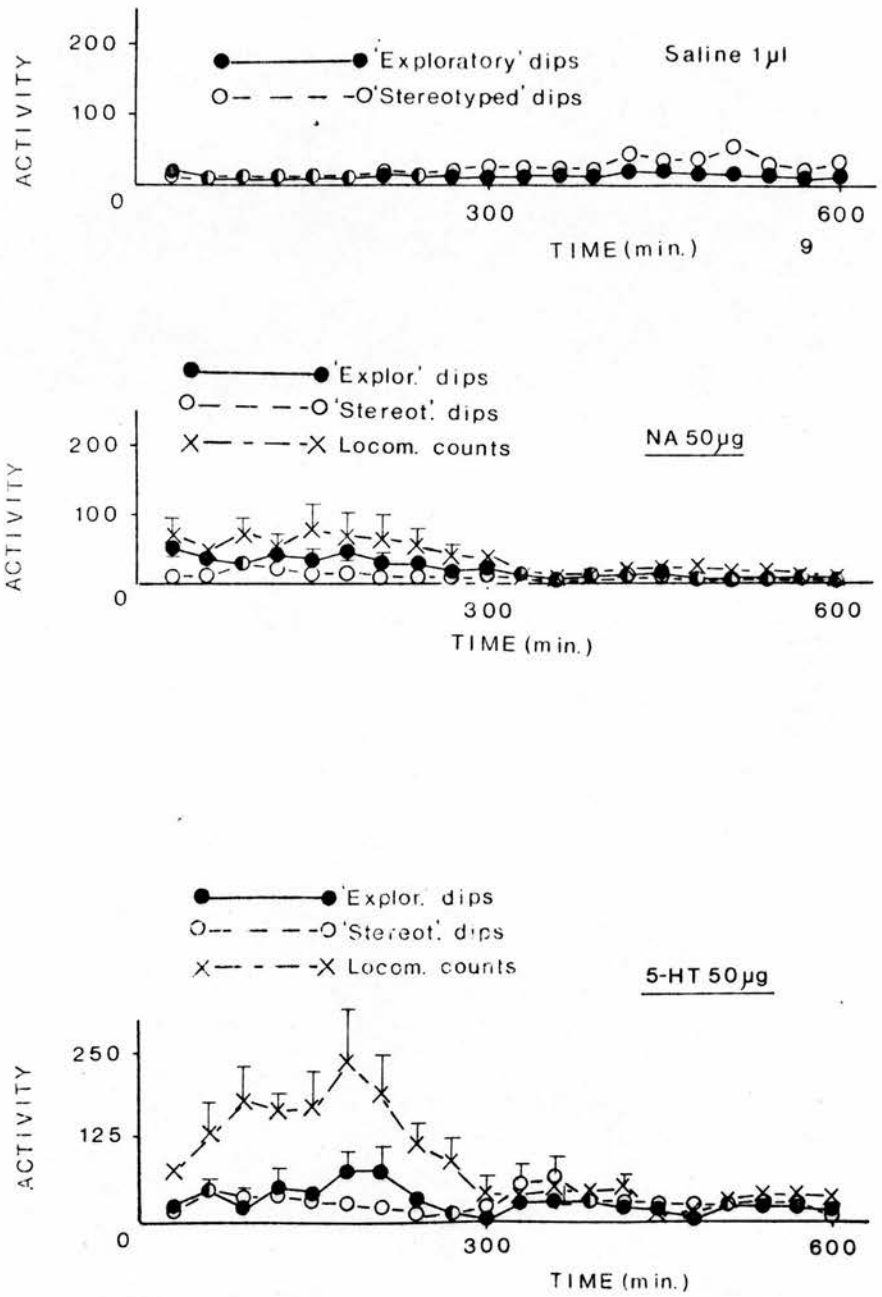

FIG. 63: Behavioural response in the hole-board apparatus following bilateral injection of 1 µl saline or 50 µg L-noradrenaline (as the hydrochloride salt) or 50 µg 5-hydroxytryptamine (as the bimaleinate salt) into the accumbens-nuclei of nialamide-pretreated rats. Each point represents mean response ± S.E.M. of 6 or 7 rats during each successive 30 min. interval following the intracerebral injection. Animals were pre-treated with nialamide 100 mg/kg i.p. 2 hours before the intracerebral injection.

TABLE 39: Behaviour in the hole-board apparatus following application of 1 µl physiological saline or 50 µg L-noradrenaline hydrochloride or 50 µg 5-HT bimaleinate into the accumbens nucleus on each side. Each animal was pretreated with 100 mg/kg nialamide i.p. two hours before the intracerebral injection. Figures show mean response ± S.E.M. during successive 30 min. intervals after the intracerebral injection of 5-6 rats.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts.

TIME INTERVAL (min)	0 - 30			30 - 60		
TREATMENT	S	E	LOC	S	E	LOC
Saline	12 ± 5	17 ± 5	42 ± 23	11 ± 7	9 ± 3	6 ± 4
NA 50 µg	12 ± 5	49 ± 13	70 ± 25	12 ± 4	33 ± 13	42 ± 12
5-HT 50 µg	14 ± 2	21 ± 3	73 ± 14	47 ± 19	45 ± 11	136 ± 46
TIME INTERVAL (min)	60 - 90			90 - 120		
TREATMENT	S	E	LOC	S	E	LOC
Saline	14 ± 10	11 ± 7	16 ± 9	12 ± 7	12 ± 8	16 ± 8
NA 50 µg	30 ± 14	33 ± 13	68 ± 27	19 ± 8	39 ± 18	47 ± 21
5-HT 50 µg	36 ± 13	22 ± 7	182 ± 58	39 ± 12	49 ± 30	166 ± 27
TIME INTERVAL (min)	120 - 150			150 - 180		
TREATMENT	S	E	LOC	S	E	LOC
Saline	13 ± 5	9 ± 5	25 ± 11	12 ± 7	7 ± 5	17 ± 9
NA 50 µg	15 ± 7	36 ± 17	82 ± 33	15 ± 5	43 ± 21	71 ± 35
5-HT 50 µg	29 ± 12	39 ± 13	168 ± 48	30 ± 9	74 ± 31	233 ± 76
TIME INTERVAL (min)	180 - 210			210 - 240		
TREATMENT	S	E	LOC	S	E	LOC
Saline	14 ± 5	8 ± 4	7 ± 5	16 ± 7	11 ± 5	20 ± 9
NA 50 µg	8 ± 3	31 ± 14	67 ± 35	12 ± 3	28 ± 13	53 ± 28
5-HT 50 µg	21 ± 7	72 ± 39	182 ± 62	17 ± 4	35 ± 16	115 ± 33

(Contd.)

TABLE 39: continued

TIME INTERVAL (min)	240 - 270			270 - 300		
TREATMENT	S	E	LOC	S	E	LOC
Saline	20 ± 12	11 ± 5	7 ± 4	25 ± 14	10 ± 5	26 ± 15
NA 50 µg	7 ± 3	15 ± 9	40 ± 16	12 ± 3	18 ± 4	29 ± 8
5-HT 50 µg	16 ± 4	15 ± 4	81 ± 34	22 ± 4	7 ± 3	41 ± 25
TIME INTERVAL (min)	300 - 330			330 - 360		
TREATMENT	S	E	LOC	S	E	LOC
Saline	24 ± 9	10 ± 4	19 ± 11	23 ± 7	12 ± 4	16 ± 9
NA 50 µg	8 ± 3	14 ± 8	9 ± 4	4 ± 1	10 ± 3	10 ± 4
5-HT 50 µg	54 ± 28	25 ± 14	33 ± 21	63 ± 32	28 ± 10	54 ± 24
TIME INTERVAL (min)	360 - 390			390 - 420		
TREATMENT	S	E	LOC	S	E	LOC
Saline	22 ± 7	11 ± 5	24 ± 15	46 ± 13	18 ± 4	31 ± 14
NA 50 µg	8 ± 4	6 ± 2	8 ± 3	11 ± 5	16 ± 5	15 ± 4
5-HT 50 µg	28 ± 6	27 ± 8	46 ± 15	29 ± 8	22 ± 11	53 ± 18
TIME INTERVAL (min)	420 - 450			450 - 480		
TREATMENT	S	E	LOC	S	E	LOC
Saline	36 ± 11	19 ± 4	21 ± 9	38 ± 12	19 ± 7	21 ± 11
NA 50 µg	13 ± 7	10 ± 3	21 ± 8	7 ± 4	17 ± 7	25 ± 5
5-HT 50 µg	27 ± 10	18 ± 5	18 ± 2	25 ± 10	7 ± 3	16 ± 5
TIME INTERVAL (min)	480 - 510			510 - 540		
TREATMENT	S	E	LOC	S	E	LOC
Saline	54 ± 16	19 ± 8	22 ± 9	30 ± 5	16 ± 8	31 ± 12
NA 50 µg	7 ± 3	11 ± 3	14 ± 5	7 ± 3	10 ± 3	14 ± 4
5-HT 50 µg	23 ± 10	24 ± 10	29 ± 10	30 ± 15	20 ± 10	42 ± 15

(Contd.)

TABLE 39: continued

TIME INTERVAL (min)	540 - 570			570 - 600		
TREATMENT	S	E	LOC	S	E	LOC
Saline	22 ± 8	10 ± 4	10 ± 2	35 ± 12	18 ± 11	32 ± 16
NA 50 µg	3 ± 1	9 ± 3	11 ± 4	5 ± 1	5 ± 2	8 ± 3
5-HT 50 µg	24 ± 7	19 ± 4	35 ± 10	12 ± 3	15 ± 5	29 ± 8

Details of the responses of individual rats can be found in the Appendix (Tables 34, 44, 45).

TABLE 40: Overall behavioural response in the hole-board apparatus during a 10 hour period following application of 1 µl physiological saline or 50 µg L-noradrenaline hydrochloride or 50 µg 5-HT bimaleinate into the accumbens nucleus on each side. Each animal was pretreated with nialamide 100 mg/kg 2 hours before the intracerebral injection. Figures show overall response of each animal during the 10 hours.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

DOSE	ACTIVITY	RAT NO.						MEAN ± SEM
		1	2	3	4	5	6	
	S	384	331	792	220	394	757	480 ± 96
	E	154	234	447	204	99	416	259 ± 58
0	T	538	565	1239	424	493	1173	739 ± 150
	S/T	0.71	0.59	0.64	0.52	0.80	0.65	0.65 ± 0.04
	LOC	117	411	595	334	124	-	316 ± 91
	S	332	237	192	122	237		224 ± 35
	E	705	342	725	183	208		433 ± 119
NA	T	1037	579	917	305	445		657 ± 139
50µg	S/T	0.32	0.41	0.21	0.40	0.53		0.37 ± 0.05
	LOC	1100	-	1404	243	270		754 ± 294
	S	649	599	558	721	360	623	585 ± 50
	E	861	694	307	786	513	366	* 588 ± 93
5-HT	T	1510	1293	865	1507	873	989	1173 ± 124
50µg	S/T	0.43	0.46	0.65	0.47	0.41	0.63	0.51 ± 0.04
	LOC	2535	2042	1306	1665	1364	-	** 1782 ± 229

* p = 0.026

**p = 0.008

(Mann-Whitney U test)

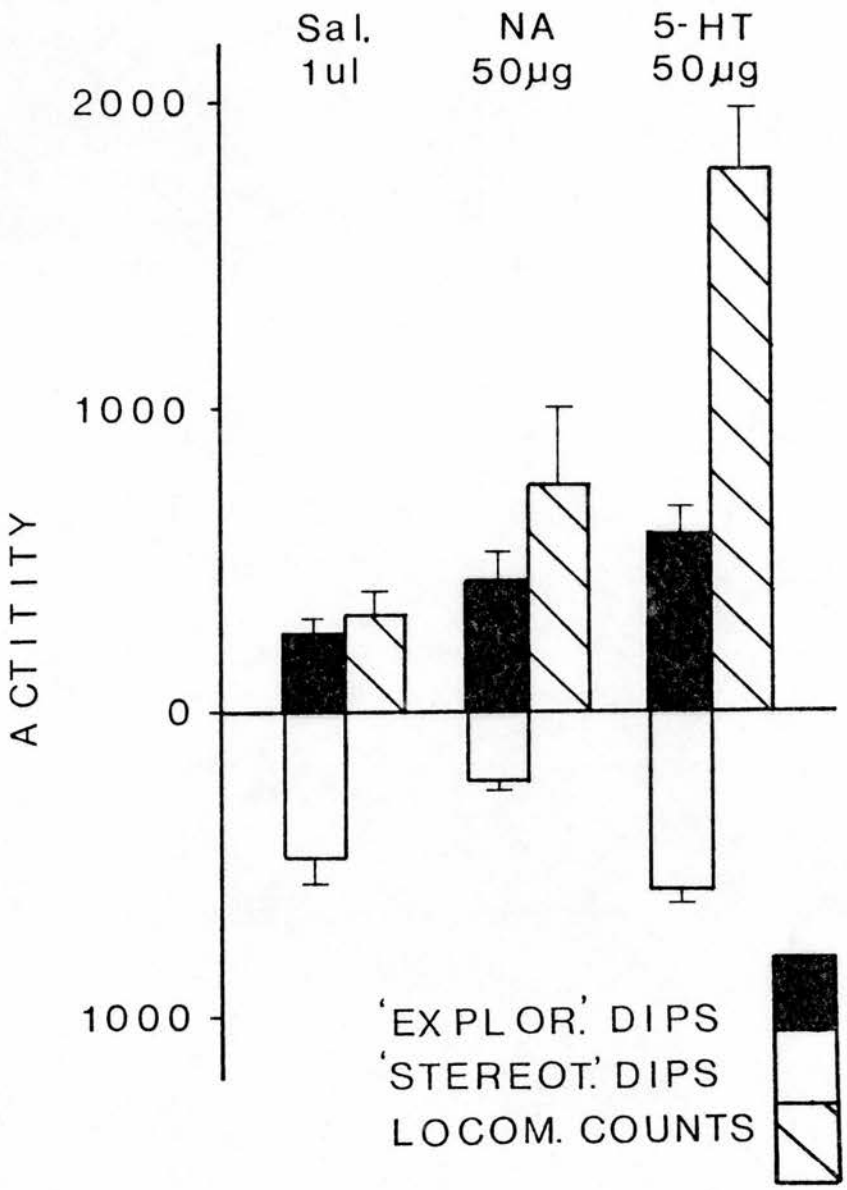

FIG. 64: Overall response in the hole-board apparatus following bilateral injection of 1 µl saline or 50 µg L-noradrenaline (as the hydrochloride salt) or 50 µg 5-hydroxytryptamine (as the bimaleinate salt) into the accumbens nuclei. Each column represents overall mean activity ± S.E.M. of 6 or 7 rats during the 10 hour period immediately following the intracerebral injection. Each animal was pretreated with nialamide 100 mg/kg i.p. 2 hours before the intracerebral injection.

(vi) Effect of bilateral injection of 50 µg 5-hydroxytryptamine bimaleinate into the accumbens nuclei in nialamide pretreated rats

50 µg 5-HT bimaleinate was injected into the nucleus accumbens on each side two hours after pretreatment with 100 mg/kg nialamide i.p. and the behaviour studied on the hole board for 10 hours.

When injected into the accumbens nuclei, 5-HT produced somewhat variable behavioural responses (Figs.63c,64, Tables 39,40). The most prominent response was a locomotor activity stimulation which began within 30 min. and was usually over within 5 hours. The locomotor activity was in most cases sporadic. A less marked stimulation of dipping behaviour of both types also occurred. On visual observation, the behavioural response showed marked differences from that seen with DA injection into the nucleus. The animal's movements appeared less coordinated and less purposeful. The body was flattened on the floor of the hole-board as it moved around. Rearing never took place. Intense sniffing was observed.

The increase in locomotor counts compared with saline-injected controls was highly significant ($p = 0.008$) and the increase in "exploratory" dipping was also significant ($p = 0.026$).

(vii) Effect of injection of 50 µg 5-hydroxy-tryptophan bimaleinate into the caudate nuclei in nialamide pretreated rats

50 µg 5-HT bimaleinate was injected into the caudate nuclei on each side two hours after pre-treatment with 100 mg/kg nialamide i.p. and behaviour studied on the hole board for 10 hours.

Here again the 5-HT injections produced variable results. In some animals no striking response occurred whereas in others a moderate stimulation of both forms of dipping behaviour and locomotor activity occurred (Figs. 65c,66, Tables 41,42). The time-course of the response was similar to that of 5-HT injected into the accumbens nuclei. The animals' postures were not abnormal and some rearing behaviour was observed.

When compared with control animals which had 1 µl saline injected into the caudate nuclei, the increase in "stereotyped" dipping and exploratory dipping were not statistically significant, while the increase in locomotor counts was significant ($p = 0.030$).

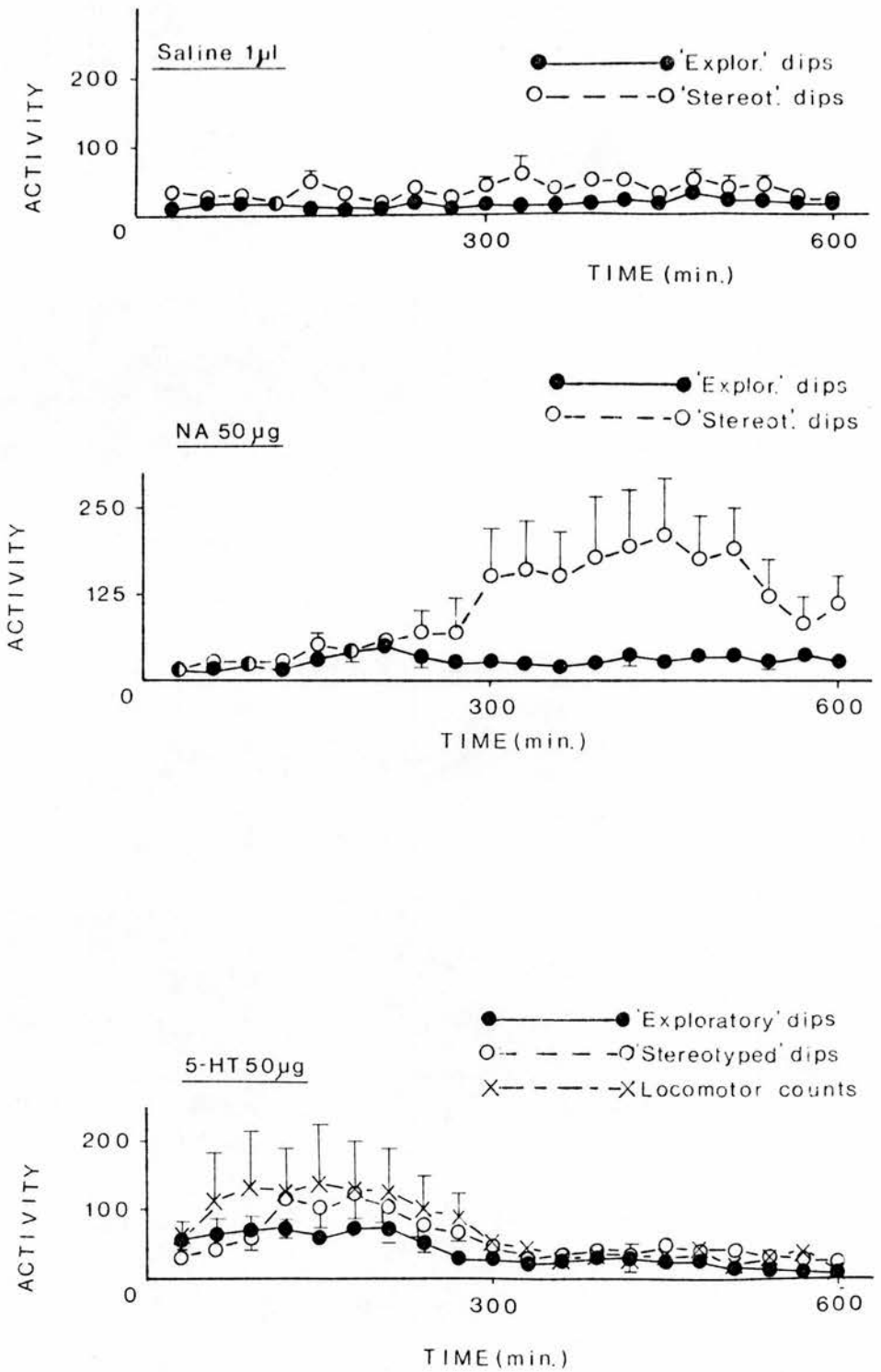

FIG. 65: Behavioural response in the hole-board apparatus following bilateral injection of 1 µl saline or 50 µg L-noradrenaline (as the hydrochloride salt) or 50 µg 5-hydroxytryptamine (as the bimaleinate salt) into the caudate-putamen nuclei of nialamide-pretreated rats. Each point represents mean response ± S.E.M. of 6 or 7 rats during each successive 30 min. interval following the intracerebral injection. Animals were pretreated with nialamide 100 mg/kg i.p. 2 hours before the intracerebral injection.

TABLE 41: Behaviour in the hole-board apparatus following application of 1 µl physiological saline or 50 µg L-noradrenaline hydrochloride or 50 µg 5-HT bimaleinate into the caudate nucleus on each side. Each animal was pretreated with 100 mg/kg nialamide i.p. two hours before the intracerebral injection. Figures show mean response ± S.E.M. during successive 30 min. intervals after the intracerebral injection of 6-7 rats.

S - "Stereotyped" dips; E - "Exploratory" dips; LOC - Locomotor counts.

TIME INTERVAL (min)	0 - 30			30 - 60		
TREATMENT	S	E	LOC	S	E	LOC
Saline	11 ± 4	34 ± 10	46 ± 9	27 ± 10	18 ± 7	5 ± 4
NA 50 µg	15 ± 5	14 ± 5	26 ± 9	25 ± 10	13 ± 5	24 ± 12
5-HT µg	28 ± 8	57 ± 10	66 ± 23	39 ± 15	64 ± 26	113 ± 71
TIME INTERVAL (min)	60 - 90			90 - 120		
TREATMENT	S	E	LOC	S	E	LOC
Saline	29 ± 6	15 ± 5	21 ± 16	21 ± 4	13 ± 4	12 ± 5
NA 50 µg	18 ± 8	17 ± 5	24 ± 8	25 ± 13	14 ± 3	54 ± 15
5-HT 50 µg	62 ± 26	69 ± 25	136 ± 83	117 ± 54	72 ± 17	123 ± 73
TIME INTERVAL (min)	120 - 150			150 - 180		
TREATMENT	S	E	LOC	S	E	LOC
Saline	50 ± 17	10 ± 3	13 ± 6	31 ± 10	7 ± 4	13 ± 5
NA 50 µg	48 ± 18	29 ± 10	54 ± 17	42 ± 11	39 ± 17	69 ± 13
5-HT 50 µg	107 ± 52	58 ± 15	139 ± 89	118 ± 53	69 ± 16	131 ± 76
TIME INTERVAL (min)	180 - 210			210 - 240		
TREATMENT	S	E	LOC	S	E	LOC
Saline	14 ± 3	5 ± 2	9 ± 6	41 ± 14	18 ± 9	21 ± 17
NA 50 µg	62 ± 10	51 ± 16	45 ± 12	72 ± 30	34 ± 11	29 ± 12
5-HT 50 µg	106 ± 38	72 ± 25	120 ± 67	82 ± 23	52 ± 19	105 ± 52

(Contd.)

TABLE 41: continued

TIME INTERVAL (min)	240 - 270			270 - 300		
TREATMENT	S	E	LOC	S	E	LOC
Saline	24 ± 5	8 ± 3	8 ± 4	47 ± 12	13 ± 5	13 ± 7
NA 50 µg	121 ± 53	25 ± 10	46 ± 15	148 ± 73	27 ± 8	24 ± 9
5-HT 50 µg	67 ± 14	28 ± 9	92 ± 35	43 ± 11	28 ± 11	48 ± 12
TIME INTERVAL (min)	300 - 330			330 - 360		
TREATMENT	S	E	LOC	S	E	LOC
Saline	58 ± 26	12 ± 4	13 ± 9	36 ± 13	16 ± 5	12 ± 5
NA 50 µg	159 ± 85	25 ± 5	37 ± 16	152 ± 69	20 ± 8	43 ± 9
5-HT 50 µg	37 ± 9	23 ± 13	45 ± 13	34 ± 13	23 ± 13	31 ± 11
TIME INTERVAL (min)	360 - 390			390 - 420		
TREATMENT	S	E	LOC	S	E	LOC
Saline	51 ± 13	16 ± 7	12 ± 7	50 ± 10	20 ± 5	18 ± 10
NA 50 µg	182 ± 92	24 ± 10	46 ± 13	195 ± 85	37 ± 14	54 ± 13
5-HT 50 µg	39 ± 13	29 ± 12	35 ± 9	34 ± 9	30 ± 18	28 ± 15
TIME INTERVAL (min)	420 - 450			450 - 480		
TREATMENT	S	E	LOC	S	E	LOC
Saline	32 ± 13	14 ± 4	16 ± 7	48 ± 15	31 ± 9	28 ± 13
NA 50 µg	211 ± 86	27 ± 12	60 ± 17	175 ± 69	34 ± 9	41 ± 12
5-HT 50 µg	50 ± 15	23 ± 8	36 ± 9	42 ± 14	24 ± 9	44 ± 10
TIME INTERVAL (min)	480 - 510			510 - 540		
TREATMENT	S	E	LOC	S	E	LOC
Saline	41 ± 16	22 ± 7	35 ± 14	47 ± 11	20 ± 7	37 ± 17
NA 50 µg	191 ± 63	36 ± 9	79 ± 13	121 ± 62	27 ± 10	67 ± 21
5-HT 50 µg	41 ± 13	15 ± 5	19 ± 4	35 ± 15	13 ± 4	28 ± 8

(Contd.)

TABLE 41: continued

TIME INTERVAL (min)	540 - 570			570 - 600		
TREATMENT	S	E	LOC	S	E	LOC
Saline	27 ± 12	16 ± 5	17 ± 7	19 ± 9	9 ± 5	10 ± 6
NA 50 µg	82 ± 44	35 ± 13	62 ± 14	110 ± 46	26 ± 8	51 ± 13
5-HT 50 µg	28 ± 9	12 ± 3	35 ± 9	25 ± 12	10 ± 3	11 ± 5

Details of the responses of individual rats can be found in the Appendix (Tables 39, 46, 47).

TABLE 42: Overall behavioural response in the hole-board apparatus during a 10 hour period following application of 1 µl physiological saline or 50 µg L-noradrenaline hydrochloride or 50 µg 5-HT bimaleinate into the caudate nucleus on each side. Each animal was pre-treated with nialamide 100 mg/kg 2 hours before the intracerebral injection. Figures show overall response of each animal during the 10 hours.

S - "Stereotyped" dips; E - "Exploratory" dips; T - Total number of dips; S/T ratio - ratio of "stereotyped" over total dips; LOC - Locomotor counts.

TREATMENT	ACTIVITY	RAT NO.							MEAN ± SEM
		1	2	3	4	5	6	7	
Saline 1 µl	S	543	832	394	1249	494	732		707 ± 126
	E	369	66	133	327	440	561		316 ± 77
	T	912	898	527	1576	934	1293		1023 ± 148
	S/T	0.60	0.93	0.75	0.79	0.53	0.57		0.69 ± 0.06
	LOC	352	22	99	-	424	752		330 ± 130
NA 50 µg	S	1280	6924	678	2169	1059	1452	1569	*** 2162 ± 812
	E	599	918	398	334	500	390	723	552 ± 80
	T	1879	7842	1076	2503	1559	1842	2292	2713 ± 873
	S/T	0.68	0.88	0.63	0.87	0.68	0.79	0.68	0.74 ± 0.04
	LOC	989	741	917	-	1019	561	1383	** 935 ± 114
5-HT 50 µg	S	1214	445	294	840	1583	729	2876	1140 ± 334
	E	1676	1418	244	329	1114	848	395	775 ± 173
	T	2290	1863	538	1169	2697	1577	3271	1915 ± 351
	S/T	0.53	0.24	0.55	0.72	0.58	0.46	0.88	0.57 ± 0.08
	LOC	811	4882	336	1267	876	956	632	* 1394 ± 591

* p = 0.030
** p = 0.018
*** p = 0.014

(Mann-Whitney U test)

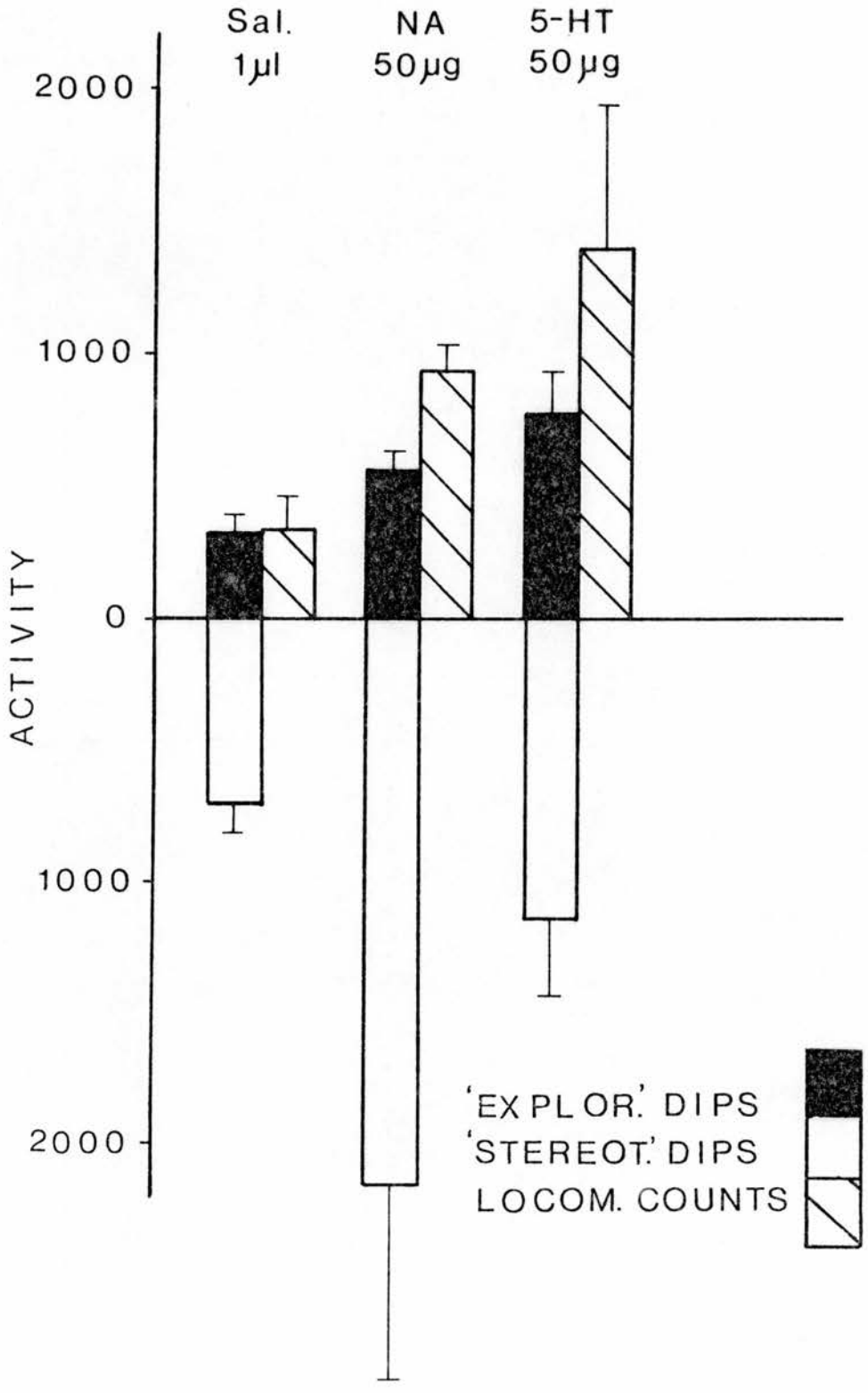

FIG. 66: Overall response in the hole-board apparatus following bilateral injection of 1 µl saline or 50 µg L-noradrenaline (as the hydrochloride salt) or 50 µg 5-hydroxytryptamine (as the bimaleinate salt) into the caudate-putamen nuclei. Each column represents overall mean activity ± S.E.M. of 6 or 7 rats during the 10 hour period immediately following the intracerebral injection. Each animal was pretreated with nialamide 100 mg/kg i.p. 2 hours before the intracerebral injection.

DISCUSSION

In this study the behavioural responses of rats to drugs and to other manipulations have been studied using an automated hole-board technique for the simultaneous monitoring of exploratory, stereotyped and locomotor activity. The interest in the role of monoamine systems in the regulation of the three forms of behaviour stems from an attempt to relate changes in these behaviours in animals to the behavioural changes in patients with psychotic illness. A better understanding of the way in which monoamine systems regulate the behaviours should increase our understanding of the behavioural changes in psychotic illness and of how these changes can be modified in the clinical situation. Both in animals and in man these behaviours occur and change in association with each other; in spite of this most previous work with animals has concentrated on only one or occasionally two of the behaviours in question. With respect to stereotactic manipulations of central monoamine systems exploratory behaviour has been largely ignored.

An attempt has been made to rectify these problems by studying all three behaviours simultaneously, and this has allowed a closer examination of the relationships between the three behaviours as well as examination of the roles of monoamine systems in their mediation. Techniques which monitor a variety of behaviours simultaneously are probably more likely to provide animal models of psychotic illness than those which depend on observation of just one aspect of behaviour.

Monitoring of behavioural responses The hole-board method was originally introduced as a technique for the study of exploratory behaviour of small animals (Boissier and Simon, 1962). Several workers subsequently have used it for this purpose with both rats and mice (e.g. Boissier and Simon, 1964; U'Prichard and Steinberg, 1972; Ljungberg and Ungerstedt, 1976). The frequency of head-dipping into holes has been shown to be a valid and reliable method for measuring exploratory activity (File and Wardill, 1975a,b; Makanjuola, 1976; Makanjuola et al. 1977a). Automated recording of hole-dipping has been achieved using infra-red detection techniques (Boissier and Simon, 1967; Ljungberg and Ungerstedt, 1976; Makanjuola, 1976; Makanjuola et al. 1977a), and simultaneous automated recording of locomotor activity, using a technique similar to that in the present study, introduced by Ljungberg and Ungerstedt (1976). The major advance in the application of this methodology for behavioural measurements in the study with which the author has been involved has been the differentiation of stereotyped from exploratory patterns of behaviour on the hole-board. The method relies on recognition of a form of stereotyped behaviour by the repetitive (stereotyped) patterns of hole-dipping in contrast to the random patterns which have been found to be associated with exploration. The quantitative differentiation of "exploratory" from "stereotyped" hole-dipping activity has been described on page 61 .

"Exploratory" and "stereotyped" hole-dipping do not encompass the complete expression of exploration and stereotypy but are facets of these activities which may be exhibited by forms of behaviour other than hole-dipping e.g. behaviour under the influence of apomorphine. However, it has been shown that changes in the overall intensities of these two types of hole-dipping, accompanied by changes in their relative proportions (as represented by the S/T ratio, the ratio of stereotyped over total dips) do reflect changes in the two forms of behaviour (Makanjuola, 1976; Makanjuola et al. 1977a). A fuller discussion of other methodological considerations concerning the hole-board apparatus appears later (page 235).

Behavioural responses to amphetamine

Amphetamine administered to adult male rats led to the expected behavioural responses (page 82). The lower doses (2 and 4 mg/kg DL-amphetamine sulphate) caused a moderate stimulation predominantly of "exploratory" dipping and locomotor activity as well as of sniffing and rearing movements. At the highest dose used (8 mg/kg), after an initial stimulation of exploratory dipping and locomotor activity, the levels of these two activities actually fell to below control levels (Fig. 16) whereas "stereotyped" dipping increased markedly. In previous experiments (Makanjuola, 1976; Makanjuola et al. 1977b) it had been found that a still higher dose of amphetamine (16 mg/kg) induced an intense form of stereotyped behaviour ("non-dipping stereotyped behaviour") which was not registered by the hole-board technique (page 146).

Amphetamine is thought to accentuate the activities of both dopaminergic and noradrenergic systems, and to a lesser extent of serotonergic systems, mainly by causing transmitter release from neuronal terminals (page 23). Information regarding the relative roles of different monoamine systems in the amphetamine-induced response may be derived from observation of the effects on the response of drugs with selective actions on different systems.

Modification of response to amphetamine by haloperidol. Haloperidol is a potent antagonist of DA receptors (Andén et al. 1970a; Seeman et al. 1976) but also has relatively weaker α-adrenoceptor blocking properties (Andén et al. 1970a). This drug at low doses markedly inhibited spontaneous exploratory and locomotor activity (page 90) and also when given previously, reduced the amphetamine-induced stimulation of exploratory, locomotor and stereotyped behaviours. The degree of inhibition by haloperidol of both spontaneous and amphetamine-induced activities was dose-related. In this respect, amphetamine-induced stereotypy was more susceptible to the inhibitory actions of haloperidol than the other two behaviours. Furthermore it was shown (Fig. 21) that the effects of increasing dosages of haloperidol on the amphetamine response mirrored the effects of reduction in doseage of amphetamine without neuroleptic pretreatment. These findings provide good evidence that DA systems play a major role in the mediation of "spontaneous" exploratory and locomotor activity as well as amphetamine-induced

stimulation of exploratory, locomotor and stereotyped behaviours.

The other two monoamine receptor blockers, phenoxybenzamine and methysergide, did not produce such marked effects on the amphetamine response in spite of the relatively high doses of the antagonists employed.

Modification of behavioural response to amphetamine by phenoxybenzamine. Phenoxybenzamine is a potent α adrenoceptor antagonist (Andén et al. 1967b; Doxey et al. 1972) with predominantly post-synaptic actions (Doxey et al. 1972; Starke et al. 1975) but it also has antagonist actions at 5-HT, histamine and acetylcholinergic receptors (Nickerson and Collier, 1975). It is accordingly difficult to draw conclusions from the effects of this drug on the amphetamine-induced response particularly in view of the fact that the animals pretreated with this drug were invariably ill-looking and lethargic. Relatively severe peripheral autonomic effects must be taken into consideration. In confirmation of other reports (Fuxe and Ungerstedt,1970;Rolinski and Scheel-Kruger, 1973; Ljungberg and Ungerstedt, 1976) it was found that pretreatment with phenoxybenzamine reduced the locomotor and exploratory stimulation induced by amphetamine, leaving "stereotyped" dipping relatively unaffected. These results seem to indicate that noradrenergic systems exert facilitatory influences on exploratory and locomotor behaviour. This evidence is, however, suspect in view of the lack of selectivity of action of phenoxybenzamine. However, the conclusion is supported by the

similar reduction of amphetamine- and L-DOPA-induced locomotor and exploratory stimulation produced by prior dopamine-β-hydroxylase inhibition (page 35). It would have been of interest to study the effects of phenoxybenzamine on the response to a higher dose of amphetamine which on its own would have led to a more clear-cut stereotyped response. However, in view of the obvious undesirable side-effects of the α-adrenoceptor antagonist further studies were not undertaken. Other workers have observed that α-adrenoceptor blockade with a variety of agents including phenoxybenzamine, phentolamine and aceperone has little or no effect on drug-induced stereotypy (page 35).

Modification of behavioural response to amphetamine by methysergide Methysergide is a potent antagonist at 5-HT receptors (Garattini and Valzelli, 1965; Aghajanian et al. 1975). This agent produced a moderate potentiation of the response to 4 mg/kg DL-amphetamine sulphate affecting all three behavioural parameters under study (page 98). This observation contradicted one other report that 5-HT receptor blockade reduces the locomotor response to amphetamine (van Riezen, 1972), although most studies have failed to demonstrate any effect of such blockade on apomorphine- or amphetamine-induced stereotyped behaviour (page 35). This failure by other workers to observe any effects by 5-HT receptor antagonists on stereotyped behaviour may be because the potentiation observed in this study is not marked and thus may remain undetected in experiments relying on

visual observation only. Even in the present study the potentiation of stereotyped dipping was not particularly intense and did not achieve statistical significance.

Behavioural responses to apomorphine

Apomorphine, a potent agonist at DA receptor sites, (page 26) induced responses identical to those found in a previous study (Makanjuola, 1976; Makanjuola et al. 1977b). While the exploratory and stereotyped actions monitored by hole-dipping were actually inhibited, the behavioural effects observed visually were consistent with a stimulation of exploratory behaviour at low doses and of stereotyped behaviour at high doses, both forms of behaviour involving principally motor activities involved in gustation and olfaction. Although other workers have claimed that apomorphine stimulates locomotor behaviour at lower doses (Fuxe and Ungerstedt, 1970; Ljungberg and Ungerstedt, 1976), in the present study the stimulant effects on locomotor activity were not marked. In fact most animals under the influence of apomorphine tended to crawl slowly around the hole-board, much more of its activity being directed towards sensory stimulation which mainly involved the olfactory and gustatory senses.

Behavioural responses to 5-Methoxy,-N,N,-dimethyltryptamine

5-Methoxy,-N,N,-dimethyltryptamine (5-MEODMT), a putative agonist at 5-HT receptors (Grahame-Smith, 1971b; Green and Grahame-Smith, 1976), produced behavioural responses very different to those induced by apomorphine

and amphetamine. In accord with the findings of other workers, the drug induced a bizarre hyperactivity syndrome involving an unco-ordinated hyperactivity, hyperextension of the body, sniffing and repetitive head movements. Inco-ordination was the most prominent feature of the syndrome unlike those induced by apomorphine and amphetamine at least with lower doses, in which activity was co-ordinated and explicable in terms of motivation towards specific ends e.g. locomotion or exploration. Whichever dose of 5-MEODMT was employed within the tested range of 2.5 - 10 mg/kg the behavioural response was qualitatively the same. The drug is known to be a potent hallucinogen (Grahame-Smith, 1971b).

It would have been useful to study the response to noradrenergic receptor stimulants. However there are no readily available β-adrenoceptor agonists which can penetrate the CNS on systemic administration. Clonidine, an α-adrenoceptor agonist (Andén et al. 1970b) also has effects (probably indirect) on DA and 5-HT systems (page 28) and more importantly exerts actions on presynaptic α-adrenoceptors as well as postsynaptic receptors. This presynaptic activity has been proposed as an explanation of the drug's sedative effects (page 28). In preliminary studies using the drug it was found that clonidine caused locomotor depression and ataxia. Apparently in an attempt to overcome these presynaptically-induced sedative actions some workers have pretreated animals with reserpine which would have the effect of eliminating presynaptic mechanisms by depleting monoamine

neurones of their transmitters. Under these circumstances clonidine has been found to potentiate the locomotor stimulant effects of apomorphine in mice (Andén and Strombom ,1974; Pycock et al. 1977) or to stimulate exploration of an open field in rats that were also given a small dose of apomorphine (Fuxe and Ungerstedt, 1970) but to have no effect on apomorphine-induced stereotypy (Pycock et al. 1977). On the face of it these results would seem to indicate that activation of postsynaptic α -adrenoceptors leads to a stimulation of locomotor and probably exploratory behaviour in the presence of some dopaminergic receptor activation. Perhaps a more definitive study would be to investigate the behavioural effects of clonidine in animals that had been pretreated with a dopamine- β - hydroxylase inhibitor which would preferentially decrease presynaptic noradrenergic neuronal activity. In these circumstances clonidine should stimulate locomotor activity.

Behavioural responses to inhibitors of neuronal transmitter reuptake mechanisms

Attempts were made to study the effects of facilitation of activity in individual monoamine systems by employing a variety of inhibitors of neuronal transmitter re-uptake of varying degrees of selectivity on individual monoamines.

In support of widely-reported observations (page 38), the tricyclic antidepressant drugs studied, desmethylimipramine (DMI) and chlorimipramine (CMI) were found to give rise to behavioural depression in rats. It is

interesting that the drug GEA 654 tended to stimulate locomotor and exploratory behaviour, although not to a statistically significant degree. The effect of this drug was examined because it has been reported to be a very selective inhibitor of 5-HT uptake with virtually no effects on DA or NA uptake (Astra, 1976) and also because it is structurally different from the conventional tricyclic drugs (Fig. 30). It also appears to be devoid of other types of action (Astra, 1976). Chlorimipramine is somewhat more effective in inhibiting neuronal uptake of 5-HT than of NA (page 38) and in the experiments on rats caused less behavioural sedation than desmethylimipramine which is more selective against NA uptake (page 38). It will be recalled that the α-adrenoceptor agonist clonidine also causes behavioural sedation, although this action of clonidine may be presynaptically-induced (page 187). These observations could therefore be interpreted as indicative of a primary inhibitory effect on behaviour by noradrenergic systems.

The effects of postsynaptic α-adrenoceptor blockade on spontaneous as well as amphetamine-induced behaviour (page 184) are inconsistent with such an interpretation. However, the effects of such drugs on spontaneous activity are not particularly marked (Ljungberg and Ungerstedt, 1976) and the possible influence of peripheral side-effects as well as actions on other neurones have been discussed above (page 184). The widely-observed reduction of amphetamine-induced exploratory and locomotor stimulation by these drugs is not so easily

dismissed, but interactions of NA systems on a primarily DA-mediated response could well result in different effects from those of primary stimulation of NA-mediated systems on that behaviour through other mechanisms.

Behavioural responses to selective inhibitors of neuronal DA uptake "LRCL 5182" is a potent inhibitor of DA uptake with no activity against NA or 5-HT uptake, no effects on monoamine release and no anticholinergic activity (Pullar, personal communication). This drug, like amphetamine, induced a marked stimulation of "exploratory" dipping and locomotor activity at a low dose (10 mg/kg) and a marked stimulation of "stereotyped" dipping and "non-dipping" stereotyped behaviour at higher doses. In contrast to amphetamine, however, the higher dose of LRCL 5182 also caused a further marked stimulation of locomotor activity. Indeed this is the only drug so far tested in the hole-board apparatus which produced both intense stereotypy and locomotor stimulation simultaneously.

Benztropine, originally thought to exert its clinical effects in the treatment of Parkinsonism through its anticholinergic properties (See Barbeau, 1962; Calne, 1970), also has potent inhibitory actions against neuronal DA uptake (Coyle and Snyder, 1969; Horn et al. 1974). This drug caused a marked stimulation of hole-dipping of both types and, particularly at a lower dose (2.5 mg/kg of the mesylate salt), of locomotor activity. It is difficult to be certain whether it is the anticholinergic or the dopamine uptake-inhibiting properties of the drug

that is the more important for the behavioural response to benztropine. A variety of anti-Parkinsonian agents which have both anticholinergic and dopamine-uptake inhibiting properties (including benztropine) have been shown to cause locomotor and exploratory stimulation in rats and mice (e.g. Arnfred and Randrup, 1968; Scheel-Kruger, 1970; Kulkarni and Dandiya, 1974). Anticholinergic drugs which lack significant DA uptake inhibiting properties such as atropine and scopolamine (Horn et al. 1971) on their own do cause exploratory and locomotor stimulation at relatively high doses, but are not so effective in inducing stereotyped behaviour (Arnfred and Randrup, 1968; Scheel-Kruger, 1970; Blozovski and Blozovski, 1973). It is presumed that these effects are mediated through a functional interaction between acetylcholinergic and dopaminergic systems (see Bartholini et al. 1973). On the other hand LRCL 5182, a dopamine uptake inhibitor without anticholinergic properties was found in this study to produce intense stimulation of exploratory, locomotor and stereotyped behaviours. Nomifensine, a potent inhibitor of DA as well as NA uptake, also stimulates all three behaviours whereas substances such as desmethylimipramine, which inhibit NA uptake but not DA uptake (page 38), do not. It is therefore very likely that both the dopamine uptake-inhibiting properties and the anticholinergic properties of benztropine play a part in mediating the response.

Conclusions drawn from behavioural effects of systemically-administered drugs

The one major conclusion that can be drawn from the studies with systemic drug administration so far discussed is that dopaminergic systems play a major role in the mediation of all three behaviours under consideration, namely exploration, stereotypy and locomotion. Drugs, with stimulant actions, either direct (apomorphine) or indirect (amphetamine or DA uptake inhibitors), on DA receptors markedly stimulate all three behaviours whereas drugs (e.g. haloperidol) which inhibit DA systems can in sufficient dose completely block spontaneous and drug-induced exploratory, stereotyped and locomotor behaviours.

Manipulations of the noradrenergic and serotonergic systems produce much less marked effects. α -noradrenergic receptor blockade may reduce spontaneous locomotor and exploratory behaviour and does significantly reduce but not abolish amphetamine-induced stimulation of exploratory and locomotor behaviour. On the other hand stimulation of noradrenergic systems by selective noradrenaline uptake inhibitors or by clonidine also seems to reduce activity.

Manipulation of 5-HT systems produced opposite results to those of the NA systems. Inhibition of 5-HT re-uptake with GEA 654 caused a slight (not statistically significant) stimulation of exploratory and locomotor behaviour whilst direct activation of serotonergic receptors by 5-methoxy-N.N.-dimethyltryptamine produced a bizarre hyperactivity syndrome which however is probably mediated at the level of the brain stem or

spinal cord (page 51). The 5-HT receptor antagonist methysergide potentiated amphetamine-induced locomotor, exploratory and probably also stereotyped behaviour.

It may be that NA and 5-HT systems directly exert minor effects on exploratory and locomotor behaviour as well as possibly stereotyped behaviour, perhaps interacting with DA inputs at postsynaptic receptors in terminal areas. The NA and 5-HT systems may also exert their effects through modification of activity in DA systems at a presynaptic level (and probably also vice versa). Interactions between the monoamine systems have been discussed in detail on page 19.

The induction of 'supersensitivity' in dopaminergic systems

An apparent supersensitivity to the behavioural effects of amphetamine was demonstrated in two separate experiments, one by chronic pretreatment with amphetamine itself and the other by chronic pretreatment with a dopamine receptor antagonist.

Results from a study of the response to amphetamine by animals with unilateral 6-hydroxydopamine lesions of the nigro-striatal pathway had indicated that repeated weekly treatment with amphetamine tended to lead to an increasing behavioural response to the drug (Makanjuola, 1976). If this was so then the interpretation of results from behavioural studies involving repeated treatment with amphetamine (and possibly other drugs) would be made difficult, even if statistically valid experimental procedures such as a "Latin-Square" design

were used. In a further investigation reported here it has been shown that repeated weekly administration of amphetamine does indeed lead to an increase in the behavioural responses to the drug, the overall effect being similar to that of the administration of higher doses of amphetamine in naive animals. Similar observations have been described in another study (Segal and Mandell, 1974). An earlier report (Lewander, 1968b) of the development of tolerance to the stereotypy-inducing response to amphetamine may be explained by the more frequent (twice daily) and larger doses of amphetamine used (16 mg/kg DL-amphetamine sulphate). This potentiation of the motor effects of amphetamine is in contrast to the widely-reported observations of tolerance to certain other actions of amphetamine with chronic treatment, in particular the anorexogenic, hyperthemic and cardiovascular effects (Harrison et al. 1952; Brodie et al. 1970; Lewander, 1974).

The reasons for this potentiation of the motor effects of amphetamine are not clear. In the first place the augmentation may not be related to amphetamine administration at all, but to independent changes within the animal's central nervous system, for example as the animal grows older. It has been demonstrated that brain levels of all three monoamines increase with age even in the adult rat (Karki et al. 1962; Gunne, 1963). Whether this increase in transmitter levels is reflected in functional changes is uncertain, however. The augmentation of the effects of amphetamine may occur within

only six days of the first dose of the drug (Rebec and Groves, 1976) and definite changes were observed in some animals at the second treatment in the present study. Also in the present study when rats were given saline injections on three successive occasions at weekly intervals the behavioural responses to amphetamine administered a week after the last saline injection was smaller than that of animals that had been given amphetamine on the three occasions before that (Figs. 18, 19). If ageing of the animal during the period of chronic treatment was an important factor in the phenomemon then it would have been expected that the behavioural responses to amphetamine in the two groups of rats would have been the same. The same argument applies regarding the effects of previous exposure to the apparatus.

In the study reported in this thesis, the animals were isolated during the period of behavioural study and on each experimental day animals that had been studied earlier were kept out of contact with those that had not yet been studied. However, the animals were put back together at the end of each experimental day, at a time when some of the animals were still under the influence of the amphetamine. It is known that the stimulant and the lethal actions of amphetamine are potentiated when the drug is given to mice in a crowd as opposed to isolated mice (Chance, 1946; Greenblatt and Osterberg, 1961). It seems unlikely that such an effect would carry over to the extent that this potentiation could still occur when an animal was studied in isolation a week later. Segal and Mandell (1974) performed their studies on rats that remained isolated throughout.

There is some evidence to suggest that increased sensitivity of dopaminergic receptors may be responsible for the potentiation of amphetamine effects following repeated treatments. Rebec and Groves (1976) have demonstrated that long-term amphetamine administration to rats resulted in a potentiation of the depression of activity of neurones in the caudate-putamen induced by acute administration of amphetamine or apomorphine. Since the site of action of apomorphine is held to be post-synaptic (page 26) these results would suggest that the augmentation of the motor response to apomorphine and amphetamine is due to an increase in sensitivity of dopaminergic receptors. Tenner et al. (1977) observed an attenuation of apomorphine-induced rotation in animals with unilateral 6-hydroxydopamine-induced lesions of the nigro-striatal pathway following long-term amphetamine administration. They suggested that the attenuation might be due to increased sensitivity of DA receptors in the contralateral neostriatum. Increased binding of tritiated haloperidol and apomorphine to DA receptors from the caudate-putamen has been demonstrated following exposure of a preparation of such receptors to DA at high concentrations in vitro (Seeman et al. 1978). These workers suggest that this increase in receptor binding following expsoure to DA may reflect increased sensitivity of the receptors and that a similar mechanism might lead to the potentiation of the behavioural effects of agonist drugs; both amphetamine and apomorphine would cause increased occupation of the post-synaptic receptor sites

by agonist substances (DA in the case of amphetamine or the drug itself in the case of apomorphine) and thus lead to increased receptor sensitivity.

Behavioural supersensitivity to the effects of amphetamine and apomorphine has been previously observed following long-term neuroleptic pretreatment (Ungerstedt et al. 1975; Christensen et al. 1976; Smith and Davis, 1976; Nielsen et al, 1977; Ungerstedt and Ljungberg, 1977), or even after a single dose of a neuroleptic agent after the acute effects of the neuroleptic have worn off (Christensen et al. 1976; Ungerstedt et al. 1975).

In the present study, contrary to the report of Smith and Davis (1976) and in agreement with that of Ungerstedt and Ljungberg (1977), it was found that chronic haloperidol administration produced no effects on spontaneous activity. However, chronic haloperidol administration (daily injection of 1 or 5 mg/kg i.p.) did appear to lead to a potentiation of the behavioural response to amphetamine. This potentiation was statistically significant only in the second experiment in which a higher dose of haloperidol (5 mg/kg) was employed (instead of 1 mg/kg) and a longer interval of 3 days (instead of 1 day) allowed between cessation of haloperidol administration and behavioural testing. Which of the two factors was the more important is uncertain. It has been proposed that the behavioural supersensitivity, after neuroleptic treatment, to drugs which stimulate DA systems is due to increased dopaminergic receptor sensitivity and an analogy has been made between this

situation and the apparent increase in sensitivity of DA receptors in the caudate-putamen following denervation by 6-hydroxydopamine-induced lesions of the nigro-striatal pathways (Arbuthnott, 1976).

Long-term administration of the neuroleptic agent penfluridol has been observed to lead to increased sensitivity to the locomotor effects of bilateral application of DA to the nucleus accumbens and to the stereotypy-inducing effect of application of DA to the neostriatum (Jackson et al. 1975b). Chronic haloperidol pretreatment of rats has been observed to be followed by an increase in the amount of binding of neuroleptics and apomorphine to dopaminergic receptors in the striatum; this finding was considered to provide direct evidence for the development of an increase in the sensitivity of DA receptors following chronic neuroleptic pretreatment (Seeman et al. 1978).

The development of tolerance to the tranquillizing actions of haloperidol was also noted during the course of haloperidol pretreatment; the effects of acute haloperidol administration in inducing behavioural sedation lasting for progressively shorter intervals and decreasing in intensity. These findings confirm those of other observers (Christensen et al. 1976; von Stralendorff et al. 1976; Ezrin-Waters and Seeman, 1977). Tolerance to the effects of neuroleptic drugs on the increase of DA turnover in the nigro-striatal and mesolimbic systems has also been observed (Burki et al. 1976; Scatton, 1978).

It would appear from these experimental results that we have an apparently paradoxical situation whereby chronic treatment either with dopaminergic receptor antagonists or with dopaminergic receptor agonists both appear to cause sensitization of the dopaminergically-innervated systems, this most likely being a result of the development of receptor supersensitivity. It is possible to explain the development of supersensitivity following neuroleptic treatment in terms of a homeostatic response to underactivity of those receptors in a way analogous to the compensatory supersensitivity which can develop following reduction in transmitter release from the presynaptic neurones, e.g. following denervation. Whatever the postsynaptic mechanism involved, the development of this homeostatic phenomenon would lead to tolerance to the effects of further neuroleptic administration and potentiation of the response to a dopaminergic receptor agonist. A longer time course of the reversion of the homeostatic mechanism to its normal levels than the time course of clearance of the neuroleptic after cessation of administration would account for the apparently greater potentiation of the actions of a potential dopaminergic receptor activation when these were measured at a longer interval after stopping the neuroleptic administration than when determined shortly afterwards. This would explain the greater potentiation of the amphetamine actions when the drug was tested 3 days after the chronic haloperidol pretreatment than when it was tested only one day after. It would be expected that the opposite

phenomenon would ensue following administration of an agonist drug - such treatment should lead to a sub-sensitivity and the development of tolerance to the agonist drug, instead of the sensitization that has been observed. One explanation for this discrepancy could be that binding to the DA receptor by any drug, whether agonist or antagonist, will lead to the development of supersensitivity i.e. that it is occupation of the receptor per se that produces the effect. This would fit with the findings of Seeman et al. (1978) that pre-exposure of a DA receptor preparation to high concentrations of DA in vitro leads to increased binding of both haloperidol and apomorphine to the receptors. However, other hypotheses would have to be invoked to explain the behavioural supersensitivity to dopaminergic agonists following denervation or following reserpine or tyrosine hydroxylase inhibition (Dominic and Moore, 1969; Friedman et al. 1975; Ungerstedt et al. 1975). All three procedures should result in a reduction in occupation of post-synaptic receptor sites.

Recently some interesting evidence has been advanced concerning the properties of presynaptic and postsynaptic DA receptors in the caudate-putamen (Nagy et al. 1978). According to these workers, neuroleptic agents, apomorphine (and presumably DA) bind to the postsynaptic receptor whereas the presynaptic receptors bind only apomorphine and DA but not the neuroleptics. It is presumed that the presynaptic receptors would act as autoreceptors for the homeostatic regulation of activity in the dopaminergic nerve ending.

These findings may provide an alternative explanation for the apparent paradox that pretreatment with either antagonist or agonist drugs can produce supersensitivity of DA innervated postsynaptic systems. The supersensitivity following neuroleptic pretreatment could be explained purely on the basis of the postsynaptic changes, since antagonists do not directly affect the presynaptic receptor. However, dopaminergic agonists would produce effects on the presynaptic receptors as well as the postsynaptic ones. Tolerance to the presynaptic effects would facilitate dopaminergic neuronal output and thus potentiate agonist effects synergistically. Such a theory would require that the presynaptic receptor changes would outweigh the postsynaptic changes.

The recent report of Nagy et al. (1978) showing a higher affinity of apomorphine for the presynaptic than for the postsynaptic dopamine receptors indicated that the receptors at the two sites are not identical. In consequence one might expect a difference in susceptibility of receptors at the two sites to modification by an agonist. Friedman et al (1975) have observed that the increase in the potentiation of the stereotypy-inducing actions of apomorphine by chronic reserpine pretreatment were further enhanced if either apomorphine or α-methyl-p-tyrosine were given along with the reserpine during the pretreatment. These results support the hypothesis that the potentiation of the effects of apomorphine and other DA receptor agonists might be induced through presynaptic actions.

These theories do not exhaust the possibilities regarding the aetiology of tolerance and supersensitivity in dopamine mediated systems. Various other theories exist concerning these pheonomena (Goldstein et al.1968) and in view of the relative lack of information available one cannot easily discount some of these possibilities. Extensions of investigations such as those of Seeman and his colleagues on receptor binding may provide useful information in the future. Studies of changes in adenylate cyclase in DA-innervated areas following chronic neuroleptic pretreatment may possibly provide useful information. DA-stimulated adenylate cyclase is thought to be involved in the activation of post-synaptic receptors and antagonism of the activity of this enzyme by neuroleptic drugs has been observed (Iversen and Miller, 1976). It might be expected therefore that striatal DA-stimulated adenylate cyclase activity would be increased in a situation of receptor supersensitivity. However, studies of changes in DA-stimulated striatal adenylate cyclase following 6-hydroxydopamine lesions of the nigro-striatal pathways have yielded inconsistent results (see Seeman et al. 1978).

Effects of inhibitors of monoamine uptake on the behavioural response to amphetamine and on the concentrations of amphetamine in plasma and brain

The two tricyclic antidepressant drugs employed, chlorimipramine (CMI) and desmethylimipramine (DMI) as well as GEA 654, a potent inhibitor of neuronal 5-HT

uptake, all caused a marked potentiation of the behavioural response to a small dose of amphetamine. This confirms the findings of various other workers (page 39). It had been found that tricyclic antidepressants inhibit the metabolism of amphetamine (Sulser et al. 1966; Lewander, 1968; Valzelli et al. 1968; Garattini et al. 1976) and this inhibition was proposed by these workers to be the cause of the potentiation of the behavioural effects of amphetamine although the facilitation of the actions of amphetamine through inhibition by the tricyclic drugs of the uptake of amines released from neuronal terminals by the amphetamine could not be excluded. If inhibition of the metabolism by the tricyclic agents was the important element in the potentiation, then inhibition of microsomal enzyme systems by other drugs should potentiate the behavioural response to amphetamine. It was found in this study that SKF-525A, a well-known inhibitor of microsomal enzyme (Brodie, 1958) systems did potentiate the behavioural response to amphetamine to a degree comparable with that induced by the three uptake inhibitors studied.

Furthermore all four drugs(the three uptake inhibitors as well as the inhibitor of hepatic metabolism) produced a marked elevation of plasma and brain levels of amphetamine. The abilities of the various drug treatments to potentiate the behavioural response to amphetamine was proportional in the same rank order as their abilities to potentiate the behavioural response to the amphetamine, 25 mg/kg DMI being the most effective and 25 mg/kg CMI

the least affective. Unfortunately this relationship could not be proved statistically because at the dose used DMI actually potentiated the amphetamine response to such a degree that "non-dipping stereotyped behaviour", which was not registered on the hole-board apparatus record, was a major effect. This is a response which is normally observed with very high doses of amphetamine (page 146). There was also too much variation in individual amphetamine levels, particularly in plasma.

The results of these experiments strongly support the view that the potentiation of the amphetamine response by antidepressant monoamine uptake inhibitors are related in major degree to the abilities of these drugs to inhibit the metabolism of amphetamine. It still cannot be excluded that a role may also be played by prevention of the neuronal re-uptake of released monoamines, however. It seems probable that the higher concentrations in brain and plasma of amphetamine detected following pre-treatment with the hepatic microsomal enzyme inhibitor SKF-525A as well as the tricyclic antidepressants or GEA 654 result from a decrease in the rate of metabolism because of an inhibitory action of the drugs on the hepatic microsomal system.

<u>The effects of lesions of the caudate-putamen and accumbens nuclei and the resultant modification of the response to amphetamine</u>

The distribution of DA in the four areas examined (the olfactory tubercles, accumbens nuclei, caudate-putamen

nuclei and cortex) in sham-lesioned animals corresponded to the findings of other workers(page 238). The 6-hydroxydopamine injections induced severe degrees of DA depletion which was maximal in the target areas. There was also considerable DA depletion in adjoining areas, this being most marked in the olfactory tubercles following injection of the neuroleptic into the accumbens nuclei. NA depletion in these areas was not marked. A detailed discussion of the distribution of the catecholamines in the selected brain areas as well as of the effects of the 6-OHDA injection appears later (page 238).

Striking effects were obtained following stereotactic manipulation of DA terminals within the nucleus accumbens and caudate-putamen. Bilateral 6-hydroxydopamine (6-OHDA) lesions of the accumbens nuclei produced a decrease of spontaneous, as well as of amphetamine-induced, locomotor and exploratory activity. Amphetamine-induced stereotyped head movements, gnawing and biting were potentiated but amphetamine-induced sniffing was eliminated. This potentiation of the more extreme aspects of stereotyped behaviour may be due to an elimination of competing influences towards locomotion and exploration.

6-OHDA lesions of the caudate-putamen also produced striking behavioural changes. These animals showed a marked reduction in spontaneous locomotor and exploratory behaviour as well as relatively slow weight gain associated with reduced food intake which was more marked the greater the degree of neostriatal DA depletion. The most prominent behavioural effect, however, was a

complete elimination of amphetamine-induced stereotypy - such as stereotyped hole-dipping, stereotyped head movements and gnawing and biting. Amphetamine-induced sniffing was not so affected and was if anything potentiated. Under the influence of amphetamine the majority of animals engaged in a high level of locomotor activity, even at the high dose of 16 mg/kg, which in control animals as well as animals with nucleus accumbens lesions produced intense stereotyped behaviour with an inhibition of locomotion and exploration. However, certain animals with severe striatal DA depletions were virtually immobile (except for intense sniffing) under the influence of amphetamine shile others with equally severe degrees of DA depletion and equally low body weight engaged in a high level of locomotor activity without any hole-dipping. This immobility following amphetamine administration in certain animals with lesions in the caudate-putamen did not appear to be related to the degree of incidental DA depletion in the nucleus accumbens, since this depletion was not greater than in those which responded with marked locomotor stimulation.

Animals with less severe degrees of striatal DA depletion engaged in a high degree of both locomotor activity and "exploratory" dipping under the influences of both doses of amphetamine used (4 and 16 mg/kg).

It is tempting to speculate that a minimal level of dopaminergic input into the neostriatum is essential for all forms of motor activity including those which are mediated primarily from other areas. Below a certain

level the more complex activities such as hole-dipping and other exploratory activities may be unable to occur while simpler activities such as locomotor activity can still take place. With more extensive depletion all actions may cease, and the basic actions of feeding and drinking, which have been gradually becoming increasingly impaired as DA depletion increased, are finally halted and death eventually occurs. However, the striatal DA concentrations in the groups of animals which showed no motor stimulation under the influence of amphetamine were no different from the concentrations in those animals in which marked locomotor activity (without exploratory dipping) was observed (Table 26). Different degrees of DA depletion in other areas, which inevitably occur after 6-OHDA lesions of the caudate-putamen particularly in the nucleus accumbens which appears to be involved in locomotor activity and exploration, also do not provide an explanation for the presence or lack of a motor response, since there were no apparent differences in the degree of such depletion between the two groups.

Certain animals with bilateral 6-OHDA lesions of the caudate-putamen engaged in tight circling activity under the influence of amphetamine, presumably because of an imbalance in the degree of DA depletion achieved on each side. (The responses of such animals were excluded from analysis of the results of bilateral lesioning.) Animals with lesions in the nucleus accumbens never displayed such tight turning behaviour with amphetamine administration. Similarly, when DA

was injected unilaterally into the striatum (on occasions when bilateral injection could not be performed) tight turning in a direction contraversive to the injection site occurred. Unilateral injection into the nucleus accumbens did not produce turning and indeed did not produce any abnormality in locomotor activity. These observations support the findings of Kelly and Moore (1976) which showed that inbalance in neostriatal dopaminergic activity was necessary for circling behaviour to occur.

Electrolytic lesions of the accumbens nuclei Even severe electrolytic lesions of the accumbens nuclei were ineffective in altering the behavioural responses following saline or amphetamine administration. (Behavioural tests were started 10-14 days after induction of the lesions.) Naylor and his colleagues (page 44) have claimed that "stereotyped sniffing" induced by amphetamine and apomorphine is eliminated by such lesions. (They did not report any effects of these lesions on locomotion and exploration.) No such changes were observed in this study.

It would have been expected that spontaneous and amphetamine-induced locomotor and exploratory behaviour would be reduced by such lesions in view of the observed effects of 6-hydroxydopamine-induced lesions of the nucleus. It has been demonstrated in this study with 6-OHDA lesions that quite severe depletions of DA in the nucleus, presumably indicative of marked reductions in the number of functional dopaminergic neurones, are

required before consistent behavioural changes would occur. Such a relation between DA concentration and behavioural changes was also noted by Ungerstedt and Marshall (1975). It may be that the degree of damage to the nuclei by the electrolytic lesions in the present study was inadequate. However, even lesions involving up to 80% of both nuclei were ineffective in altering behaviour. Perhaps more important is the fact that electrolytic lesions damage all types of neurones associated with the nucleus, in contrast to the 6-OHDA injection which induced selective damage to DA terminals. Damage to other neuronal inputs may compensate for the damage to DA inputs, particularly if all three monoamine systems as well as other systems interact in the nucleus (see page 19). Cell bodies, efferent neuronal terminals and afferent fibres and fibres of passage are all damaged by the electrolytic lesion.

At this stage it would be useful to examine in detail a recent paper by Naylor and his colleagues (Costall et al. 1977) in which were reported the results of studies related to those which had been already performed in the project reported in this thesis. Bilateral 6-hydroxydopamine lesions were induced in various areas of the nigro-striatal and mesolimbic dopaminergic systems.

In the study by Naylor and his colleagues it was found that the effects of lesions varied according to the time after operation. It is difficult to decide which effects to accept as representing the primary

result of the lesioning. Initial effects seen in the first few days after operation and which thereafter disappear may tend to be regarded as non-specific effects even though they may not be present in control animals but could equally well be a true lesion effect which becomes reversed by compensatory processes in that system or others which interact with it. Similarly a more persistent effect which arose only after a delay of several days could reflect compensatory changes to the original functional change induced by the lesion.

In their study Costall et al. found that anteriorly placed bilateral 6-OHDA-induced caudate-putamen lesions reduced amphetamine- and apomorphine-induced biting but centrally placed lesions reduced amphetamine-induced biting only. Globus pallidus lesions (which also caused a marked fall in caudate-putamen DA levels) initially potentiated apomorphine- and amphetamine-induced biting but after a week led to a reduction in this response. Amphetamine-induced hyperactivity was potentiated. Lesions of the substantia nigra or ascending DA pathways, both of which caused substantial reductions in mesolimbic as well as neostriatal DA content, caused a permanent potentiation of apomorphine-induced biting. Lesions of the ascending DA pathways caused a slight but permanent reduction of amphetamine-induced biting, while substantia nigra lesions caused an initial potentiation of amphetamine-induced biting and hyperactivity.

Lesions in the nucleus accumbens reduced the duration of amphetamine-induced hyperactivity and potentiated

apomorphine-induced biting. Amphetamine-induced stereotyped sniffing was markedly and permanently reduced. Lesions of the olfactory tubercles enhanced the hyperactivity response to both drugs and potentiated apomorphine but not amphetamine-induced biting. Lesions of the central nucleus of the amygdala reduced both amphetamine-induced sniffing and biting as well as apomorphine-induced biting.

This study by Naylor and his colleagues lends strong support to their contention that different DA innervated regions in both neostriatal and mesolimbic areas mediate different forms of drug-induced stereotyped behaviour (page 45) as well as hyperactivity. There was also a suggestion that different areas may mediate the same stereotyped response to different drugs. The important element which may at least partly explain the widely discrepant claims of different groups of workers concerning the mediation of stereotyped behaviour is that of "stereotyped sniffing". Costall and his colleagues have claimed (page 45) that this component of stereotyped behaviour is mediated from the accumbens nucleus and olfactory tubercle. In this study they showed that 6-OHDA lesions of the accumbens nucleus led to a reduction in amphetamine-induced sniffing and a "potentiation of apomorphine-induced sniffing to biting". Other workers have also demonstrated reduction of amphetamine-induced sniffing and potentiation of apomorphine-induced sniffing following 6-OHDA lesions of the nucleus accumbens. (Kelly and Iversen, 1976). The so-called high intensity

component of stereotypy - licking, biting and gnawing - seems to be associated more with the nigro-striatal pathway. The significance of the abolition of the high intensity component of stereotypy following lesions of the central nucleus of the amygdala is uncertain since application of agonist drugs to this area is ineffective (page 47).

Unfortunately Naylor and his colleagues by their very method of assessing stereotyped behaviour exclude the two components of stereotypy (the sniffing activity component and the biting-licking-gnawing component) as distinct entities. According to their system of assessment any marked increase in sniffing would not warrant a particularly high stereotypy rating. Decreases in sniffing without changes in the high intensity component of gnawing, biting and licking would not warrant any change in stereotypy rating. It would be useful if these two forms of stereotypy (sniffing, and gnawing, biting and licking) were scored separately, as these workers did in some of their earlier studies. One other problem with the concept of "stereotypyed sniffing" as a distinct entity is the fact that with some lesions apomorphine-induced "sniffing" could be "potentiated into biting". This suggests rather that the two components exist as a continuum as was originally suggested (Schiorring, 1971). Naylor and his colleagues have demonstrated that certain drugs can selectively induce or inhibit one of the two components of stereotypy (Costall et al. 1975a, 1975b). There is some reason to

consider sniffing behaviour as exploratory in nature, since it involves intense sensory stimulation and is invariably accompanied by locomotor stimulation. It is only when the "licking-biting-gnawing" stereotypy is occurring that locomotion stops.

It is rather worrying that in the study of Naylor and his colleagues some lesions produced changes in amphetamine response which were not mirrored by opposite changes with apomorphine as should be expected following a 6-OHDA lesion (page 42); for example the effects of anterior caudate-putamen and globus pallidus lesions on stereotyped biting and the potentiation of the hyper-activity response following olfactory tubercle lesions. This discrepancy would be explained if the claims of Naylor et al. that different areas mediate the effects of the two drugs is true. That claim requires further substantiation.

These findings of Costall et al. (1977) are in broad agreement with most of the observations made in the study reported in this thesis concerning the effects of 6-OHDA lesions of the accumbens nuclei and caudate putamen.

In conclusion the results observed following 6-OHDA lesions of the accumbens nuclei and caudate-putamen areas in the present study, though not supported by those from electrolytic lesions of the accumbens nuclei (possibly for the reasons already discussed - page 208), indicate that different behavioural responses are mediated from the two DA-rich terminal areas. The nucleus accumbens is concerned with the mediation of exploratory and loco-

motor behaviour as well as sniffing, which I consider to be a feature of exploratory behaviour. Stereotyped behaviours, on the other hand, are mediated from the caudate-putamen. It also seems likely that a minimum level of DA input into the caudate-putamen is necessary for any form of behaviour to occur.

It would be interesting to study the behavioural effects following selective lesions of noradrenergic and serotonergic terminals in these areas. Such studies should provide information regarding the functional interactions of the three monoamine systems in these areas. It might be possible to induce selective destruction of noradrenergic neurones in discrete areas of the brain using 6-hydroxydopamine injections following inhibition of uptake of the 6-OHDA into dopaminergic neurones with benztropine or some other drug with potent inhibitory properties against DA but not NA uptake. 5-HT depletion could be achieved using the neurotoxic dihydroxytryptamines (Breese et al. 1975).

Having obtained significant information from the effects of discrete lesioning of different DA-innervated areas, it follows that studies of the responses to selective stimulations of these areas should provide further evidence in support of those findings.

Responses following stereotactically-controlled injections of monoamine transmitters into the accumbens nuclei and caudate-putamen areas

The results obtained following direct application of monoamine transmitters into the accumbens nuclei and caudate-putamen areas strongly support the findings following stereotactic 6-hydroxydopamine-induced lesions of these areas.

Methodological points related to this study are discussed on page 241.

Dopamine injected into the caudate-putamen in nialamide-pretreated rats produced a marked dose-related stimulation "stereotyped" dipping, and at the highest dose (50 µg) "non-dipping stereotyped behaviour" consisting of side-to-side as well as up and down movements of the head as well as gnawing and biting around the holes. Sniffing activity was noticeably absent. There was also a moderate stimulation of "exploratory" dipping and locomotor activity, more marked at the highest dose of DA (50 µg). This stimulation of exploration and locomotion may have been caused by diffusion of the injected material into the neighbouring accumbens nuclei. Widespread diffusion of injected DA along a concentration gradient has been demonstrated by autoradiography.Fog & Pakkenburg(1971).

Very different results followed bilateral application of DA into the accumbens nuclei of nialamide-pretreated rats. A marked stimulation of locomotor activity and "exploratory" dipping was recorded. Intense continuous sniffing and frequent rearing were also noted. The

response to DA applied to the accumbens nuclei was not convincingly demonstrated to be dose-related, however. There was no great difference in the intensity or character of the behavioural response induced by the three highest doses of DA employed (12.5, 25 and 50 µg of dopamine hydrochloride) although there was a slight trend towards an increase in dipping activity with increasing dosage. Locomotor counts were maximal with 12.5 µg. A dose of 5 µg produced a variable response, ranging from none (compared to saline-treated animals) to a near maximal response. This situation is consistent with an all-or-none response, with recruitment occurring at the dose of 5 µg and thereafter no great increase. It may be that because the accumbens nucleus is relatively small all neurones within it would tend to be affected by a dose of the transmitter slightly above the threshold, any further increase in dosage would not produce any further increase in response. If this were so it would still be expected that increasing the DA dose would prolong the behavioural response, since concentrations of DA would be maintained at or above threshold for a longer period of time. This, however, was not the case. Other workers have claimed that the response is dose-related (Pijnenburg and van Rossum, 1973; Jackson et al. 1975; Costall et al, 1975b). These workers employed the same dose range as in the present study. The discrepancies are therefore inexplicable. The moderate stimulation of "stereotyped" dipping which was observed particularly

with the highest dose may be due to diffusion of DA into the neighbouring caudate-putamen areas.

The response to DA applied to either area was completely blocked by systemic administration of haloperidol, a potent antagonist at DA receptors (Andén et al. 1970a; Seeman et al. 1976). The response from the accumbens nucleus was much more susceptible to the action of haloperidol than that from the caudate-putamen. We have observed in the M.R.C. Brain Metabolism Unit that the dose of haloperidol required to control the symptoms of mania is generally lower than that which causes extrapyramidal symptoms. This observation supports the hypothesis that dopaminergic neurones projecting to the nucleus accumbens mediate the antipsychotic effects of neuroleptics whereas nigro-striatal neurones mediate their extrapyramidal effects (page 8). However, these differences in susceptibility to the effects of haloperidol by the two nuclei are somewhat at odds with the effects on the response to systemically administered amphetamine (page 92). In that case haloperidol was more effective in blocking amphetamine-induced stereotyped behaviour than locomotor and exploratory behaviour. It would have been of interest to study the actions of noradrenergic and serotonergic receptor antagonists on the DA response. Other workers have found that α - or β - adrenoceptor antagonists are relatively ineffective in inhibiting these responses (Pijnenburg and van Rossum, 1973; Jackson et al. 1975). The 5-HT receptor antagonist cyproheptadine was also ineffective (Costall et al.1976).

Noradrenaline applied to the nucleus accumbens in nialamide pretreated rats caused only a slight stimulation of locomotor and exploratory behaviour in the hole-board apparatus which was not statistically significant; other workers have reported a moderate locomotor stimulation (Pijnenburg and van Rossum, 1973; Jackson et al. 1975), which did not occur in the absence of pretreatment with a monoamine oxidase inhibitor (Pijnenburg et al.1976).

Noradrenaline applied to the caudate-putamen induced a moderate stimulation of "stereotyped" dipping, although other workers have failed to observe any response following application of NA (Costall et al. 1974: Jackson et al. 1975). The stimulation of stereotyped dipping observed was not particularly intense, and it is possible that such relatively mild stereotypy would not be picked up by the visual monitoring techniques employed in the other studies. It is likely that the stimulation of "stereotyped" dipping by NA is mediated through stimulation of DA receptors. Direct evidence for this might be provided by observation of the effects of dopaminergic or noradrenergic receptor blockers on the response. Another possibility is that the response is mediated indirectly through actions of NA on the vascular supply to the neostriatum. This seems unlikely since if this were the case it would be expected that a behavioural response would also have been induced following application of the drug to the accumbens nuclei.

Effects on behaviour were also observed following application of 5-HT to both areas. The responses were rather variable, but certain features were prominent. When applied to the nucleus accumbens 5-HT induced a moderate locomotor stimulation, but this locomotion has characteristics different from that seen in control rats or animals stimulated with systemically applied amphetamine or DA applied into the nucleus. The locomotor stimulation was usually sporadic and the animal's body was hyper-extended with the abdomen close to the floor. Rearing did not take place. Continuous sniffing was observed. This phenomenon has some resemblance to the behaviour induced by the 5-HT receptor agonist 5-methoxy,-N,N,-dimethyltryptamine. There was also a small increase in dipping behaviour of both types but this increase was not statistically significant. These observations are at variance with other studies in which either no response to 5-HT was observed (Jackson et al. 1975) or a decrease in spontaneous locomotor activity was reported (Costall et al. 1976; Pijnenburg et al. 1976).

5-HT applicationinto the caudate-putamen elicited a stimulation of dipping behaviour of both types, predominantly "stereotyped"; locomotor stimulation was less intense and sniffing unaffected. Occasional rearing was observed. Body posture appeared normal. Jackson et al. (1975) did not observe any behavioural effects following 5-HT administration into the neostriatum.

It is surprising that these responses to 5-HT application into the two areas were not observed by other workers. Methodological differences may explain the discrepancies. Firstly, the use of closed-circuit television allowed close observation of the animals without disturbance to them. Also the hole-board apparatus used provided a somewhat different environment from those of other studies. Finally the behavioural parameters of hole-dipping may not have any parallel in these other studies which were concerned with the recording of "locomotor" activity and simple visual observation of stereotyped movements.

It must be stressed that the behavioural responses to administration of 5-HT to the two areas was quantitatively variable and in no instance as marked as with DA application. In the otherstudies referred to (Jackson et al. 1975; Costall et al. 1976; Pijnenburg et al.1976), various doses of 5-HT, including the dose employed in this study (50 µg of the bimaleinate salt), was employed without inducing behavioural stimulation.

The latent period consistently observed before the response following the intracerebral administration of the neurotransmitters requires some explanation. This delay was of the order of 30-90 min. following DA injection into either area (the delay being of relatively longer duration with lower doses of DA) and even longer following NA injection into the caudate-putamen, but was much less in the case of 5-HT administration to either area. Pijnenburg and van Rossum (1973) also noted this

delay, which however apparently did not occur when animals were not pretreated with nialamide (Pijnenburg et al. 1976). These workers suggested that the latency following intracerebral monoamine administration in nialamide pretreated animals might be a result of interaction of other monoamine systems in which activity would have been facilitated by monoamine oxidase inhibition, but they offered no direct evidence in support of this suggestion.

It is possible that high concentrations of DA (maintained high by monoamine oxidase inhibition) at receptors in the immediate area of the injection might cause an initial desensitisation. The appearance of the behavioural effects of the DA after some delay could then be due either to recovery of sensitivity of these receptors as the concentration of the amine gradually fell or to activation of receptors at a distance from the site of injection by lower concentrations of the amine reaching these more distant sites by diffusion.

A general point must be made concerning the possibility that other properties of the intracerebrally administered material might have been responsible for the responses induced. In particular, the question arises as to whether local changes in pH or osmolarity induced by the injected material might play a part. However, Pijnenburg et al. (1976) could not demonstrate behavioural effects following injection of solutions of different pH and osmolarity into the accumbens nuclei. Solutions of all three substances used in the present study, dopamine

hydrochloride, L-noradrenaline hydrochloride and 5-hydroxytryptamine bimaleinate had pH values of 4.5 ± 0.1 and at least the NA and DA solutions injected would have been of near equal acidity and molarity. However, very different behavioural responses were obtained following administration of the three substances. Therefore, it seems unlikely that molarity or pH of the injected material played any role in the behavioural responses induced, particularly in view of the relatively long delay in the appearance of the response.

The implications of these studies of the effects of monoamine transmitters applied to the two areas would appear to be quite clear. DA receptors in the nucleus accumbens are involved in the mediation of exploratory and locomotor behaviour as well as of sniffing and rearing activities. Both the latter activities may be regarded as part of the exploratory response. It seems very likely that the DA injections into the accumbens nuclei must have affected the olfactory tubercles and it might be that these behaviours were mediated from the latter site. However, injection into the more dorsal aspects of the nucleus accumbens (which would be expected to have less effect on the olfactory tubercle) did not result in a quantitatively different response from injections into the ventral aspect. Because of the relative thinness (in the dorso-ventral plane) of the olfactory tubercle it would be expected that accurate placement of injected material into that structure would be difficult. However, Pijnenburg et al. (1976) claim to have succeeded

in this; they found that DA injections into the olfactory tubercles does produce as marked a locomotor response as with injections into the nucleus accumbens.

DA receptors in the caudate-putamen, on the other hand, appear to mediate stereotyped behaviour but not sniffing, locomotion or other forms of exploratory activity. No evidence was obtained of a role for adrenoceptors in the accumbens nucleus and the mild stimulation of "stereotyped" dipping by NA applied to the caudate-putamen is probably mediated by stimulation of DA receptors but may reflect a facilitatory input into the nucleus which would play a secondary role to DA inputs. 5-HT applied to both areas produced variable stimulant effects on all three behaviours in different individual animals. These effects of 5-HT may also be mediated through direct activation of DA receptors by the 5-HT. However, the behavioural response, particularly from the accumbens nuclei, was quantitatively different (page 174) from that of DA and it therefore seems more likely that the response was mediated directly by 5-HT receptor activation.

Further evidence concerning the interactions of the three monoamine inputs in these areas might be provided by studying the effects of two (or even three) monoamines applied simultaneously. One study did show that 5-HT applied to the accumbens nuclei reversed the locomotor stimulation induced by previous application of DA therein (Costall and Naylor, 1978).

TABLE 43:

The following table gives a brief summary of the behavioural effects of the different procedures.

5-MEODMT - 5-Methoxy,-N.N.-dimethyltryptamine;
DMI - Desmethylimipramine; CMI - Chlorimipramine;
GEA 654 - A neuronal 5-HT uptake inhibitor;
LRCL 5182 - A neuronal DA uptake inhibitor;
SKF-525A - A hepatic microsomal enzyme inhibitor;
NDSB - 'Non-dipping stereotyped behaviour'- see page 146.

PROCEDURE	RECORDED BEHAVIOUR		
	Stereotyped Dipping	Exploratory Dipping	Locomotor Counts
A. SYSTEMICALLY ADMINISTERED DRUGS			
Normal Animal	0	0	0
Amphetamine 2 & 4 mg/kg	+	++	++
Amphetamine 8 mg/kg	+++	0	0
Repeated weekly Amphet.	POTENTIATION OF		
Haloperidol + Saline	-	-	-
Haloperidol + Amphetamine 8 mg/kg	DOSE RELATED ABOLITION		
Chronic Haloperidol Pretreatment	POTENTIATION OF		
Phenoxybenzamine + Amphetamine 4 mg/kg	++	0	0
Methysergide + Amphetamine 4 mg/kg	++	++	++
Apomorphine 0.75 mg/kg	-	-	+
Apomorphine 1.5 & 3.0 mg/kg	-	-	0
5-MEODMT	0	0	+
DMI + Saline	-	-	-
CMI + Saline	0	0	0
GEA 654 + Saline	+	+	+
LRCL 5182 10 mg/kg	+	++	++
LRCL 5182 20 mg/kg	+++	+	+++
Benztropine 2.5 mg/kg	+	+	+
Benztropine 5.0 mg/kg	++	++	+
DMI + Amphetamine 4mg/kg	+++	0	0
CMI + Amphetamine 4mg/kg	+++	++	++
GEA 654 "	+++	+	+
SKF-525A 15 mg/kg "	++	+	0
SKF-525A 30 mg/kg "	+++	+	0

0 - denotes normal activity level
+ - denotes stimulation of activity
- - denotes inhibition of activity

	VISUALLY OBSERVED BEHAVIOUR		
	Sniffing	Rearing	Other
	0	0	0
	++	++	
	++	0	
		AMPHETAMINE RESPONSE	
	-	-	
		OF AMPHETAMINE RESPONSE	
		AMPHETAMINE RESPONSE	
	+	0	
	++	+	
	++	-	
	++	-	Gnawing and biting
	++	-	Bizarre hyperactivity(page 106)
	++	++	
	++	0	NDSB
	+	+	
	+	0	
	++	-	NDSB
	++	+	
	++	-	
	++	+	
	++	-	

Contd.

PROCEDURE	RECORDED BEHAVIOUR		
	Stereotyped Dipping	Exploratory Dipping	Locomotor Counts
B. LESIONS			
1. 6-OHDA LESIONS			
Saline Sham Lesion			
Saline	0	0	0
Amphetamine 4 mg/kg	+	++	++
Amphetamine 16 mg/kg	+++	0	0
N.Accumbens Lesions			
Saline	0	-	-
Amphetamine 4 mg/kg	++	0	0
Amphetamine 16 mg/kg	+++	0	0
Caudate-Putamen Lesions			
Saline	-	-	-
Amphetamine 4 mg/kg	-	++	+++
Amphetamine 16 mg/kg	-	++	+++
2. ELECTROLYTIC LESIONS OF N. ACCUMBENS			
Sham Lesions			
Saline	0	0	0
Amphetamine 4 mg/kg	+	++	++
Amphetamine 16 mg/kg	+++	0	0
N.Accumbens Lesions			
Saline	0	0	0
Amphetamine 4 mg/kg	+	++	++
Amphetamine 16 mg/kg	+++	0	0
C. STEREOTACTIC INJECTIONS OF MONOAMINES			
DA into N. Accumbens	+	+++	+++
DA into Caudate-Putamen	+++	+	+
NA into N.Accumbens	0	0	0
NA into Caudate-Putamen	+	0	0
5-HT into N. Accumbens	+	+	++
5-HT into Caudate-Putamen	+	±	+

	VISUALLY OBSERVED BEHAVIOUR		
	Sniffing	Rearing	Other
	0	0	
	++	++	
	++	0	NDSB
	-	-	
	-	-	
	-	-	NDSB
	0	-	
	++	0	
	+++	0	
	0	0	
	++	++	
	++	0	NDSB
	0	0	
	++	++	
	++	0	NDSB
	+++	++	
	0	0	NDSB
	0	0	
	0	0	
	++	-	Quantitatively different behaviour (page 154)
	0	+	

The relationships between exploratory, stereotyped and locomotor behaviours

What, then, of the relationship between the three types of behaviours under consideration? In only one situation, that with systemic administration of the DA-uptake inhibitor LRCL 5182, did intense locomotor stimulation coexist with a high level of stereotyped behaviour. In all other situations when stereotyped behaviour of high intensity was taking place exploratory and locomotor behaviour did not occur. I had previously suggested (Makanjuola, 1976; Makanjuola et al. 1977b) that exploratory and stereotyped behaviour were closely related phenomena, stereotypy representing extreme stimulation of exploratory activity to the extent that the component activities involved in exploration became fragmented and repetitive (i.e. stereotyped). Drugs which induced locomotor and exploratory behaviour at low doses would induce stereotypy at high doses. Furthermore both exploratory and stereotyped behaviours involved stimulation of sensory receptors which in the case of stereotypy was extremely intense and this sensory stimulation was felt to be the central aim of both forms of behaviour.

It appears from the experiments reported in this thesis as well as the reviewed work of other workers that locomotor and exploratory behaviours are mediated through the accumbens nuclei and probably also the olfactory tubercles while stereotyped behaviour is mediated through the caudate-putamen. This would suggest that stereotyped behaviour is not in fact directly related to exploration.

But it is still necessary to explain the fact that systemically administered dopaminergic stimulants induce a pattern of behaviour in which as the dose of the drug is increased (or as tissue levels increase) locomotor and exploratory behaviours are gradually replaced by stereotyped behaviour in a manner which would suggest that it is the component activities involved in exploration that are becoming involved in the stereotypy. It was shown in this study that maximal stimulation of exploratory and locomotor behaviour were achieved with a relatively low dose of DA (12.5 µg) applied to the nucleus accumbens (in comparison to the caudate-putamen) while further increases in dose of DA applied to the caudate-putamen continued to produce increases in stereotyped response. It is probable that relatively low levels of activation of dopaminergic systems would produce a stimulation predominantly of exploration and locomotion from the mesolimbic system while increased levels of dopaminergic activation would involve the caudate-putamen more and more, this involvement being expressed in the form of stereotyped behaviour. This still does not explain the apparent inhibition of exploratory and locomotor behaviour generally observed when intense stereotyped behaviour is taking place following systemic drug administration. The inhibition may result from simple competition between the behaviours (i.e. that the behaviours are incompatible). It is also tempting to postulate an inhibitory input from the nigro-striatal system to mesolimbic DA neurones. However, there is no evidence for such an interaction,

although some projections do pass from the nucleus accumbens to the substantia nigra (Conrad and Pfaff, 1976, Nauta et al. 1978).

The behavioural response to the DA uptake inhibitor LRCL 5182 is somewhat against the hypothesis that exploratory and locomotor behaviour on the onehand and stereotyped behaviour on the other, are mutually incompatible, since this drug was able to induce intense locomotor and stereotyped behaviours simultaneously. It is possible that this drug is more selective in its effects on dopamine neurones in the mesolimbic system than the nigro-striatal system, in which case a relatively more intense stimulation of stereotypy (compared with the response to amphetamine, for instance) would be required to overcome the exploratory and locomotor stimulation induced from the nucleus accumbens. There is some evidence that some different dopaminergic agonists have selective actions on different forms of activity (Costall et al. 1975a, b.). The same could equally well apply to other agents.

Animal models of psychotic illness. Clinical relevance of studies of the roles of monoamine systems in controlling behaviour in animals.

These various observations of alterations in rat behaviour by the varied ways of manipulating monoaminergic systems in the brain raise the question of the extent to which such experiments serve to elucidate the problem of the aetiology of psychotic illness.

It was observed earlier (page 12) that in the affective disorders there were usually gross changes in exploratory and locomotor behaviours as well as the appearance of a variety of stereotyped behaviours. Animal experiments indicate that the dopaminergic systems play a major role in the mediation of these behaviours and it therefore seems very likely that disturbances of dopaminergic function are involved in the affective disorders. Whether the primary disorder lies within these dopaminergic systems or the changes in dopaminergic function are merely an expression of disturbance in some other area or areas of the brain is open to question. Various other symptoms observed in the affective disorders may also be under dopaminergic control, including food intake and sexual and reproductive function; the latter two functions may be influenced by the tubero-inpendibular dopaminergic systems (see Fuxe et al. 1970 and 1978). Indeed there are few changes in the affective disorders that cannot be interpreted in terms of changes in exploratory, stereotyped and locomotor behaviour or some other area of behaviour under dopaminergic control. Manic illness is very amenable to therapy with neuroleptic drugs which are potent dopaminergic receptor antagonists (see page 8). The neuronal NA and 5-HT reuptake blockers employed in the treatment of depressive illness may be influencing the courseof the disease through interactions with dopaminergic systems (see page 20) or through their relatively less potent effects on DA-mediated behaviour. It should be noted that these antidepressant drugs often

may be only partially effective or even ineffective (Davis and Janowsky, 1974). It would be of interest to study the effects of drugs with more selective actions on dopaminergic systems in depressive illness. The newly-introduced drug nomifensine inhibits DA as well as NA uptake (page 39). Its antidepressant actions are still being assessed clinically, but preliminary trials, though promising, have not as yet demonstrated any dramatic advantage over other antidepressants (e.g van Scheyen et al. 1977; Grof et al.1977).

Previously, amphetamine-induced stereotyped behaviour in animals has been proposed as a model for acute psychosis (Angrist and Gershon, 1974; Wallach, 1974). It is presumed that by "acute psychosis" these workers mean schizophrenia-like illness. However, amphetamine (and other drugs which stimulate DA systems) produce in animals behavioural changes which appear more in line with manic illness, since they induce an increase in coordinated exploratory and locomotor activity, with stereotyped behaviour replacing the former two activities as the amphetamine dosage is increased (page 82). This pattern of behaviour in animals is very similar to that seen in mania (page 12).

On the other hand schizophrenia involves qualitative changes in the form of behaviour (both in activity and thought) which are less easily interpreted as simple increases or decreases of normal behavioural patterns. The behavioural changes induced by 5-MEODMT (page 106) are more reminiscent of the changes in schizophrenia, in so far as the drug produces a syndrome of bizarre,

uncoordinated hyperactivity which is not readily interpretable in terms of quantitative behavioural changes. It is therefore tempting to postulate the behavioural changes induced by this drug (and perhaps other hallucinogens such as LSD) as models of schizophrenic illnesses. It must however be stressed that the aberrations induced by hallucinogens are claimed to be different from the symptoms experienced in schizophrenia (see Snyder et al. 1974). Nevertheless, the symptoms of schizophrenia in the acute stage do bear a much greater resemblance to the psychological changes induced by these drugs (Bowers and Freedman, 1966). Many hallucinogens, including 5-MEODMT (see above), LSD (see page 27) and possibly mescaline have potent agonist actions at 5-HT receptors (Aghajanian et al. 1970; Fuxe et al. 1972).

Thus it may be that disturbances of 5-HT systems feature more prominently in schizophrenic illnesses than is currently acknowledged and that the behaviour of animals following stimulation of 5-HT systems with these drugs may be useful animal models of these illnesses. The clinical usefulness of the neuroleptic drugs in schizophrenia may be used as an argument against this proposition, because of their prominent inhibitory action on transmission at dopaminergic synapses (page 8). However, these drugs can also exert antagonistic actions at 5-HT receptors (Leysen et al. 1978). It should be remembered that the behavioural response to 5-MEODMT or to stimulation of 5-HT synthesis appear to be mediated from areas of the central nervous system caudal to the

mesencephalon (Jacobs, 1976). Mediation even at the level of the spinal cord cannot be excluded. However, the question regarding involvement of 5-HT systems in schizophrenia is at least worthy of further study, in spite of the fact that the evidence for the involvement of dopaminergic systems in schizphrenia is currently much more impressive (page 8).

Turning to the observations concerning the behavioural response to direct application of monoamines to intracerebral nuclei, there are certain features which stand out and which may bear comparison with behaviour in psychotic patients. The effects of application of DA into the nucleus accumbens (page 154) bears a striking resemblance to the symptoms of mania in man. In both situations the subject makes rapid progress from one situation to the next, never stopping long enough to give each item more than a cursory examination. An analogy can be made between the behaviour of the rat darting about from hole to hole and the flight of ideas expressed by manic patients (page 12). The high level of motor activity and exploration seen in the milder forms of mania may thus be due to increased dopaminergic activity in the accumbens nuclei or other areas of the mesolimbic system. The stereotyped activity observed in the more severe forms of mania may be caused by involvement of the nigro-striatal system by increasing levels of dopaminergic activity. Evidence was presented earlier (page227) that relatively lower levels of dopaminergic stimulation were required to achieve a maximal behavioural

response from the accumbens in comparison with the caudate-putamen since a relatively small dose of DA (12.5 µg) would produce a near maximal response when administered to the nucleus accumbens, whereas further increases in dosage of DA applied to the caudate-putamen produced increasing stimulation of stereotyped behaviour. It may well be that the milder cases of mania are associated with a level of stimulation of DA systems which would induce greater behavioural effects from the mesolimbic system so that behavioural stimulation would predominantly affect locomotion and exploration. In more severe cases of mania this stimulation of DA systems would be great enough also to involve the nigro-striatal system so that stereotyped behaviour also occurs and gradually replaces the other two behaviours.

5-HT injections into the nucleus accumbens in rats led to behaviours (page 154) which were qualitatively dissimilar from those of DA injections. The behavioural responses were qualitatively as well as quantitatively abnormal. Posture was abnormal and hole-dipping on visual observation seemed to occur in uncontrolled, indecisive fashion. Sniffing behaviour was stimulated but this was not obviously directed at any particular source of sensory stimulation in the environment. It is tempting to compare this situation with schizophrenia in so far as the behaviour induced in animals by the 5-HT injection and the behaviour observed in schizophrenia are not easily rationalised in terms of motivation and appear incoordinated and haphazard. The stereotypies seen in

schizophrenia (page 13), and which also appear to be less related to sources of sensory stimulation, may in that case be caused by increased serotonergic activity in the neostriatum. 5-HT produced some stimulation of "stereotyped dipping" when injected into the caudate-putamen (page 175). These suggestions are of course, extremely speculative. More direct evidence would be needed to allow such a suggestion regarding serotonergic involvement in schizophrenia to be taken seriously. If it were so it is possible that the addition of a serotonergic receptor antagonist to medication in schizophrenics might lead to beneficial effects. It would also be of interest to study the effects of these antagonists in acute psychoses induced by hallucinogenic drugs. Perhaps also the comparison of the effects of neuroleptic drugs with differing degrees of activity against 5-HT receptors (Leysen et al. 1978) in controlling the symptoms of schizophrenia might be worthwhile.

Comments on various points of the methodologies employed in the experimental work

There are various points concerning the methodologies employed in the experimental work which are worthy of comment and discussion.

The hole-board apparatus. With the continuing experience of the different possible forms of drug-induced behaviour which were observed in the course of the experiments reported in this thesis it has become evident that the hole-board apparatus used for quantitative monitoring of

behavioural patterns had several important limitations. Perhaps the greatest limitation lies in the fact that as presently arranged not all forms of exploratory and stereotyped behaviour are automatically detectable. For example exploratory and stereotyped activity with sniffing or gnawing and biting components as seen with apomorphine and in the "non-dipping stereotyped behaviour" (page 146) seen with large doses of amphetamine and other dopaminergic agonists was not readily detected by the apparatus. Provision of pressure detectors around the edges of the holes to signal biting and gnawing activities would allow automated recognition both of this "non-dipping stereotyped behaviour" and the stereotyped behaviour of the type induced by apomorphine.

Some of the problems with the method of measuring locomotor activity have already been discussed on page 59 . It should be possible to overcome the problem of mains supply electrical interference with the locomotor activity count by technical improvements. From experience it seems important that future models of the automated hole-board apparatus should differentiate between repeated interruptions of the same overhead infra-red beams (e.g. from repetitive up and down movements of the head) from successive interruptions of different beams which would represent true locomotion. Repeated interruptions of the same beam may even provide a measure of stereotyped head movements in certain circumstances provided they occurred within the orbit of a beam.

A new automated hole-board apparatus is at present being developed which should solve some of these difficulties as well as providing other improvements on the old model. Instead of a teletype, a digital cartridge magnetic tape recorder controlled by a microprocessor is being used to record behaviour detected by the apparatus. This tape recorder can note a monitored signal within 0.5 m.sec. instead of the 400 m.sec. or more which the teletype takes to record an event. This means that signals from hole-dipping, locomotor and any other behavioural parameters can be recorded in rapid succession as they occur, with little chance of their interfering with each other in the recording process. A further set of infra-red beams set higher above the hole-board will be used to detect rearing behaviour, which has been observed in this study to accompany certain procedures. At present the two sets of infra-red beams subserving hole-dipping (page 56) are positioned at the same level beneath the hole-board floor. Because of this, if after inserting its snout into a hole an animal moves it around therein such movements could be recorded as "stereotyped" dips. It is proposed that in the new hole-board this problem will be eliminated by positioning the two sets of infra-red beams at different levels beneath the floor, one set passing close beneath the floor and the other set deeper. The detection apparatus will be set to record hole-dips only after both beams passing underneath any one hole have been interrupted and disinterrupted, so that the animal will have to insert its head deep into

the hole and withdraw it completely for a hole-dip to be recorded. Such a signal would comply more closely with the commonly held definition of a "hole-dip", which is considered to occur when the animal's snout is first inserted to a depth that the eyes reach the level of the edge of the hole and ends when it is withdrawn completely (File and Day, 1973).

A further refinement of the behavioural monitoring, already suggested, by the addition of pressure detectors around the hole edges is planned for future incorporation into the hole-board structure. I cannot envisage any practical method of automatically monitoring sniffing activity.

In the writer's opinion this envisaged version of the hole-board apparatus and its recording system probably represents the best that can be achieved without great expenditure. Beyond this point one can only picture a costly set-up involving three-dimensional scanning above and below the "hole-board" with computer analysis of the recorded signals.

The Assay of DA and NA in selected brain areas. The radio-enzymatic assay employed for analysis of dopamine and noradrenaline in brain tissue proved very sensitive (less than 50 ng/g of NA or DA could be detected). Both the DA and NA assay procedures exhibited linearity for different amounts of catecholamines within the range of D.P.M.s obtained from brain tissue samples estimated (Figs.40,41, Table 23). It was observed that noradrenaline interfered with the dopamine assay producing an increase in D.P.Ms

from the DA fraction in proportion to the amount of noradrenaline added. On the other hand increasing amounts of dopamine led to a proportionate (but smaller in comparison with the contamination of the DA fraction by NA) decrease in D.P.M.s obtained in the noradrenaline fraction. Coyle and Henry (1973) had observed the contamination by NA in the DA assay but not the reverse. No attempt was made to correct for these interferences since the assays were being used primarily to compare relatively gross changes in the same brain areas between different groups of animals. The estimates of DA in the cortex may, however, as a result of this interference be slightly overestimated whereas the NA content of the three DA-rich areas are probably underestimated.

The distribution of dopamine and noradrenaline found in the four areas examined (the olfactory tubercles, accumbens nuclei, caudate-putamen are and cortex) in animals with sham lesions of the accumbens nuclei or caudate-putamen (page 135) are in agreement with those found in other studies (Kelly et al. 1975; Kelly and Iversen, 1976; Costall et al. 1977; Verssteeg et al. 1976).

The accumbens nuclei, caudate-putamen and olfactory tubercles have, relative to other brain areas, extremely high concentrations of DA, this being highest in the caudate-putamen sample. (Fig.42 Table 24). Cortical DA levels were very low. Noradrenaline levels were much lower in the three DA-rich areas. The nucleus accumbens and cortex contained the highest amounts of NA. Much lower values were found in the olfactory tubercles and the caudate-putamen contained very little.

Effect of 6-OHDA lesions on DA and NA content. The 6-OHDA injections produced maximal DA depletion in the target areas, the caudate-putamen areas or accumbens nuclei. However, there was also substantial depletion in other contiguous areas, this depletion being particularly noticeable in the olfactory tubercles following injections into the accumbens nuclei. This is not surprising in view of the close proximity of the two structures. Other workers have made similar observations (Kelly et al. 1975; Costall et al. 1977). The greater the DA depletion in the target area the greater it was in the other areas also. An apparent depletion of cortical DA accompanied 6-OHDA lesions of the caudate nuclei. While this reduction of the DA concentration of the cortical samples may truly indicate DA depletion in the cortex since the cortical sample was taken from an area adjacent to the caudate-putamen, it is also possible that the depletion reflected the fall in DA content of caudate tissue which may have been accidentally included in the cortical sample (page 135). The desmethylimipramine pretreatment appeared to afford a great deal of protection to noradrenergic neurones since NA depletion was slight or even did not occur even in the target areas. NA depletion would of course be somewhat masked by the effect of reduction in the DA content of the samples, this would tend to cause an overestimation of NA content since it was shown that high concentrations of DA tended to interfere with the NA assay in such a way as to cause a lower d.p.m. value in the NA fraction (page 237).

It might be possible to minimize the DA depletion in areas other than the target organ by increasing the concentration of 6-hydroxydopamine, thus reducing the injection volume. Whether this would reduce the extent of diffusion of the neurotoxin away from the target areas is uncertain, particularly when the animal is pre-treated with a monoamine oxidase inhibitor.

The assay of Amphetamine in plasma and brain. Although the method for the assay of amphetamine (page 77) in plasma and brain was not extensively investigated it appeared adequate for the purpose to which it was put. Although amphetamine was still detectable below the "limits of sensitivity" set for accurate measurement, 25 ng/ml for plasma and 250 ng/g for brain, below those limits the calibration curve no longer showed linearity. This was presumed to be caused by background interference. All sample concentrations exceeded these limits.

The two major metabolites of amphetamine, p-hydroxy-amphetamine and p-hydroxynorephedrine, being phenolic in character, would not be expected to be extracted into the toluene from a highly alkaline solution (pH 12+), and these metabolites should not therefore interfere with the assay. Furthermore the trichloroacetyl derivatives of these metabolites would be expected to occupy different locations in the chromatogram from that of amphetamine itself. These aspects of the specificity of the assay procedure were not, however, investigated experimentally.

Technique for injection of monoamines into discrete brain areas. While a high degree of accuracy was achieved in the placement of the injected material, as confirmed by histological examination (page 153) certain improvements could be made to the technique.

Firstly, the injection procedure (page 67) would have been made easier if suitable stylets had been available to keep the cannulae patent in the interval between the operation to implant the cannulae and the actual injection. Stylets were in fact constructed at one stage but the animals kept pulling them out. It should be possible to design stylets which would be resistant to such interference.

The injection procedure itself involves acute penetration of overlying brain tissue by the needle, and in addition to this trauma, there was also the possibility that some of the injected material might leak into the brain tissue from the needle tip during penetration. It might be better to use cannulae which protrude into the brain and terminate within or just dorsal to the target area and which are kept patent with a stylet. Such modifications of the injection techniques have been employed by some other workers (e.g. Pijnenburg et al. 1976; Costall et al. 1975a). The foreign object inside the brain tissue might however produce a reaction from the brain tissue which would interfere with the response to an injection but this conceivably could be minimized by using relatively non-irritant materials e.g. plastic.

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APPENDIX

The following tables give details of the responses of individual rats in the hole-board apparatus during successive 10 or 30 min. intervals with different treatments. The results given in the tables are summarized in various tables in the main text which give mean responses ± standard errors of the means (S.E.M.s) during the different time intervals. These tables in the main text are referred to in brackets at the top of each table in the Appendix.

S - "Stereotyped" dips;

E - "Exploratory" dips;

LOC - Locomotor counts.

TABLE 1: Behavioural response to 1 ml/kg physiological saline i.p. (For mean response ± SEM during each time interval see Table 1 in main text).

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	14	66	60	12	47	45	3	16	42
2	23	77	53	26	25	21	11	21	7
3	11	68	44	11	17	17	16	20	18
4	26	77	62	35	45	37	30	40	48
5	13	57	30	8	24	10	18	22	22
6	23	38	40	6	9	54	4	6	45
TIME INTERVAL (min)	30 -40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	17	16	26	5	7	8	0	0	0
2	1	6	19	0	0	0	1	0	0
3	1	0	0	2	3	0	12	23	24
4	11	22	45	12	24	25	13	19	20
5	12	18	9	18	23	18	25	14	5
6	20	30	12	2	2	3	20	25	34
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	19	32	21	5	11	13	7	11	11
2	0	0	0	2	10	1	33	44	29
3	26	26	23	63	40	31	52	23	11
4	14	10	11	8	6	3	31	33	32
5	40	50	18	20	27	11	1	5	4
6	13	6	44	6	8	16	10	5	7
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	10	3	20	29	29	17	11	27	24
2	6	6	20	4	2	0	0	0	0
3	8	14	7	9	30	27	28	10	9
4	38	31	27	20	21	38	8	22	38
5	26	18	4	16	36	22	14	13	34
6	31	39	26	5	9	3	1	1	0

TABLE 2: Behavioural response to 2 mg/kg DL-amphetamine sulphate. (For mean response ± S.E.M. during each time interval see Table 1 in main text).

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	10	95	55	12	55	77	9	73	129
2	5	46	71	6	13	13	6	19	14
3	15	60	64	32	28	28	24	23	45
4	8	93	53	26	64	55	14	56	77
5	21	74	53	20	37	14	8	13	11
6	17	64	59	12	31	35	23	37	25
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	10	35	108	10	78	66	9	22	36
2	3	10	11	5	20	10	18	23	33
3	28	45	59	24	38	15	23	16	13
4	39	39	16	45	11	4	89	8	43
5	20	18	22	16	26	24	1	1	0
6	14	18	8	10	16	21	20	25	20
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	12	43	45	5	29	13	28	34	39
2	17	13	12	27	14	7	21	4	10
3	51	60	30	45	48	26	25	17	14
4	51	35	13	24	45	-	83	6	8
5	9	9	2	14	43	29	21	31	14
6	8	14	15	15	23	13	32	23	27
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	18	28	48	20	34	12	6	8	1
2	18	3	9	24	1	7	31	9	12
3	5	4	0	0	1	0	0	0	0
4	52	37	14	26	42	47	37	55	20
5	0	0	0	14	35	20	33	39	20
6	0	0	0	31	56	28	25	44	49

TABLE 3: Behavioural response to 4 mg/kg DL-amphetamine sulphate. (For mean response ± S.E.M. during each time interval see Table 1 in main text).

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	10	74	76	4	38	54	6	47	100
2	5	41	53	1	8	50	14	32	48
3	19	79	55	12	40	25	35	63	56
4	25	64	46	10	30	24	7	27	41
5	21	109	-	19	71	-	26	99	-
6	16	81	92	19	47	26	13	76	63
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	4	58	85	11	87	65	4	52	71
2	23	105	51	23	130	79	36	97	55
3	122	48	33	119	28	27	201	29	55
4	24	44	43	45	36	32	14	49	53
5	31	127	-	19	77	-	12	54	-
6	18	122	48	18	131	15	22	123	32
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	15	76	67	28	64	59	34	98	53
2	26	98	46	19	86	42	17	55	41
3	168	29	55	186	30	72	140	47	87
4	41	50	50	27	47	73	48	69	48
5	23	100	-	19	84	-	34	80	-
6	20	103	38	26	110	41	44	97	46
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	22	114	50	14	88	96	11	66	118
2	27	53	27	13	23	8	38	43	9
3	135	41	120	101	44	85	68	40	89
4	62	51	34	33	60	34	30	39	19
5	20	37	-	3	17	-	1	7	-
6	37	85	25	73	51	19	68	72	22

TABLE 4: Behavioural response to 8 mg/kg DL-amphetamine sulphate. (For mean response ± S.E.M. During each time interval see Table 1 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	18	119	72	60	111	45	163	103	41
2	40	95	30	35	23	-	137	52	-
3	26	95	29	44	67	6	1	6	0
4	23	57	45	121	88	27	118	6	0
5	50	69	24	214	96	2	440	2	0
6	17	67	47	33	87	44	92	134	50
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	335	13	25	462	1	4	482	0	0
2	115	64	28	241	35	12	309	17	6
3	23	7	0	0	1	0	0	2	0
4	209	0	0	113	0	6	281	0	0
5	526	0	0	419	0	0	300	0	0
6	245	79	29	224	46	20	216	32	9
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	469	0	0	428	5	20	356	6	4
2	289	4	0	270	10	0	277	4	0
3	97	15	0	75	5	0	158	39	4
4	314	0	0	340	0	1	348	0	0
5	201	0	0	62	3	0	248	1	0
6	275	9	6	277	11	13	289	11	88
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	340	14	21	295	37	5	258	66	97
2	236	10	5	202	8	21	145	27	18
3	168	23	17	189	36	8	160	43	5
4	336	0	0	275	4	0	312	7	2
5	616	0	0	557	0	0	473	0	0
6	242	0	0	153	41	29	146	38	9

TABLE 5: Effect of pretreatment with 20 mg/kg phenoxybenzamine hydrochloride i.p. on the response to 4 mg/kg DL-amphetamine sulphate i.p. (For mean response ± S.E.M. during each time interval see Table 9 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	10	7	6	62	47	37	74	61	31
2	17	50	59	25	68	83	65	123	70
3	9	4	7	8	9	0	6	20	36
4	3	21	31	2	1	5	12	16	21
5	3	15	35	19	39	47	13	34	61
6	9	6	14	8	4	5	3	6	8
7	2	3	17	5	6	14	8	3	10
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	65	32	36	34	33	59	19	27	62
2	67	134	70	140	109	59	162	81	47
3	4	21	44	3	11	26	19	22	36
4	53	41	25	164	18	19	132	43	41
5	3	19	90	10	30	76	5	19	81
6	1	4	2	1	8	0	4	8	8
7	49	5	19	138	24	3	83	29	0
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	24	18	49	13	13	18	14	15	21
2	138	52	17	79	60	75	89	29	39
3	10	21	37	12	10	27	21	16	22
4	113	40	66	130	25	21	148	27	25
5	4	22	74	4	24	70	9	38	85
6	1	1	0	4	5	6	11	5	4
7	65	17	7	4	5	23	19	17	31

TABLE 5: continued

TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	21	18	51	28	4	3	14	5	7
2	74	62	42	46	65	88	31	7	68
3	25	13	55	9	7	17	5	8	49
4	86	32	32	95	21	34	77	42	42
5	6	32	63	20	38	69	38	59	41
6	0	0	0	5	2	5	1	4	2
7	2	5	21	7	3	28	18	8	41

TABLE 6: Effect of pretreatment with 2.0 mg/kg methysergide Hydrogen maleinate i.p. on the response to 4 mg/kg DL-amphetamine sulphate i.p. (For mean response ± S.E.M. during each time interval see Table 9 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	13	122	111	36	136	55	22	160	67
2	18	90	88	26	94	110	43	95	83
3	25	68	98	30	59	94	73	109	90
4	43	62	40	44	51	54	80	62	75
5	10	100	127	17	76	119	11	60	138
6	40	50	90	67	42	56	56	58	77
7	11	55	76	1	5	4	32	4	24
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	35	164	58	53	158	67	86	122	87
2	82	53	94	84	76	55	60	77	48
3	103	145	102	120	98	81	90	105	118
4	119	47	38	141	64	40	99	57	33
5	14	63	174	44	97	170	42	112	185
6	28	23	30	88	27	53	85	6	33
7	55	49	36	52	50	65	77	68	45
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	123	115	84	133	121	72	202	102	64
2	56	81	66	79	91	113	116	64	89
3	52	112	98	40	99	122	78	78	96
4	88	47	25	126	42	28	67	27	27
5	30	71	149	26	48	125	50	80	71
6	85	26	38	67	44	65	48	41	33
7	61	82	56	65	55	36	63	63	45

TABLE 6: continued

TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	87	117	90	52	120	91	90	96	106
2	142	26	57	96	26	14	114	14	67
3	56	87	87	46	98	120	69	78	89
4	82	28	51	71	34	55	71	34	119
5	17	58	112	21	69	114	40	89	70
6	56	28	47	46	40	41	38	33	34
7	64	81	33	65	85	68	56	96	52

TABLE 7: Behavioural response to 0.75 mg/kg apomorphine hydrochloride i.p. (For mean responses ± S.E.M. during each time interval see Table 11 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	3	18	22	2	2	61	4	8	40
2	41	18	20	118	0	59	123	6	2
3	18	9	14	6	6	2	10	17	0
4	1	17	26	2	2	1	0	0	0
5	21	58	75	10	30	35	2	1	0
6	8	15	23	9	14	11	10	17	0
7	2	7	12	2	2	9	1	8	15
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	6	21	16	8	14	8	0	0	0
2	11	24	23	0	1	0	2	2	0
3	6	11	11	11	12	8	1	0	0
4	22	19	13	13	10	40	27	18	-
5	6	9	1	21	32	28	21	56	54
6	0	0	0	7	31	10	6	27	88
7	11	15	71	5	2	20	13	24	47
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	0	0	0	9	11	2	23	59	71
2	4	12	0	15	27	12	17	18	13
3	25	31	28	20	16	-	27	18	19
4	1	8	3	17	21	95	11	12	7
5	33	35	9	13	31	27	26	21	40
6	3	9	4	12	21	12	23	17	25
7	27	30	51	6	13	26	20	13	52
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	1	4	1	3	10	10	28	41	40
2	9	9	93	2	0	0	2	0	0
3	22	9	11	28	20	8	28	16	5
4	43	24	9	28	30	14	2	3	0
5	65	37	23	33	44	108	24	43	40
6	18	27	7	10	15	5	1	1	2
7	12	21	82	11	23	15	17	13	14

TABLE 8: Behavioural response to 1.5 mg/kg apomorphine hydrochloride i.p. (For mean responses ± S.E.M. during each time interval see Table 11 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	5	7	28	0	5	54	0	8	65
2	4	10	14	1	1	11	3	3	19
3	1	9	30	0	0	0	0	0	0
4	35	9	26	0	1	24	17	13	42
5	1	20	35	2	19	32	5	7	38
6	16	25	-	0	10	23	6	9	34
7	0	13	33	0	3	20	0	5	32
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	2	13	55	1	10	37	11	37	53
2	2	7	10	6	11	32	3	7	41
3	4	8	7	7	8	24	5	7	2
4	23	32	22	4	3	5	18	21	12
5	3	18	32	0	0	0	0	0	0
6	8	22	11	1	4	5	5	6	7
7	1	15	7	5	11	9	12	4	6
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	16	30	27	4	20	18	45	36	35
2	5	7	29	0	0	0	11	8	1
3	14	25	9	38	30	22	14	37	23
4	20	22	35	3	1	0	0	0	0
5	5	29	22	0	0	0	8	25	10
6	0	0	0	14	28	72	11	30	28
7	11	27	10	0	0	0	1	1	0
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	12	22	13	19	49	27	36	34	22
2	6	15	13	1	0	10	1	2	30
3	14	11	2	12	20	24	50	27	11
4	22	21	7	22	23	26	24	35	35
5	21	31	14	0	1	3	0	0	0
6	17	36	10	25	48	29	35	43	57
7	14	24	8	8	32	-	4	5	47

TABLE 9: Behavioural response to 3.0 mg/kg apomorphine hydrochloride i.p. (For mean responses ± S.E.M. during each time interval see Table 11 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	0	10	50	0	9	69	0	3	81
2	11	52	31	28	37	19	9	33	13
3	2	15	23	0	2	33	2	1	2
4	1	21	14	0	14	16	1	1	36
5	0	10	14	0	0	3	1	1	0
6	2	17	56	0	3	21	10	3	8
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	4	20	69	10	19	13	0	1	38
2	2	3	0	12	27	19	12	27	21
3	0	4	39	1	19	27	3	4	-
4	0	1	76	1	10	21	7	10	31
5	0	1	82	16	14	28	12	27	25
6	3	2	22	2	8	63	6	14	20
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	14	21	25	10	17	43	26	29	49
2	4	6	4	0	1	1	0	1	0
3	0	0	0	3	13	16	1	9	13
4	8	7	2	9	4	0	13	34	32
5	2	2	0	0	0	0	0	0	0
6	9	5	14	11	4	0	12	12	5
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	15	28	32	2	3	2	12	31	53
2	9	23	13	25	40	49	10	23	27
3	3	6	18	1	3	10	2	12	14
4	19	24	18	20	25	7	13	16	12
5	14	22	35	26	47	20	8	22	18
6	0	0	6	11	1	3	29	11	8

TABLE 10: Behavioural response to 2.5 mg/kg 5-Methoxy-N N-dimethyltryptamine i.p. (For mean responses ± S.E.M. during each time interval see Table 13 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	33	59	83	43	36	14	12	16	15
2	19	40	61	26	19	6	17	42	24
3	46	38	31	36	69	103	15	38	35
4	52	63	151	22	32	28	1	15	28
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	8	12	17	12	36	46	5	13	45
2	28	38	36	10	31	31	5	29	37
3	9	11	10	10	10	8	21	13	29
4	8	18	42	5	10	14	0	3	8
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	14	9	66	5	21	27	9	12	9
2	8	3	3	11	8	7	12	58	80
3	37	8	4	26	16	6	18	0	8
4	4	7	6	12	20	21	3	13	23
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	11	37	33	14	20	105	7	23	45
2	4	18	19	8	6	10	17	19	25
3	0	0	0	0	1	1	4	5	7
4	31	20	77	15	13	39	4	6	6

TABLE 11: Behavioural response to 5 mg/kg 5-Methoxy,-N N-dimethyltryptamine i.p. (For mean responses ± S.E.M. during each time interval see Table 13 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	23	31	50	39	37	26	25	49	28
2	27	44	73	35	34	25	7	27	15
3	13	25	92	26	49	75	12	47	62
4	65	59	50	16	26	5	6	21	18
5	11	49	112	19	39	58	28	31	39
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	36	30	6	21	14	24	27	12	10
2	6	9	13	1	8	10	25	5	2
3	6	16	30	3	21	24	11	12	46
4	9	5	34	1	5	17	2	3	1
5	16	36	43	8	30	57	11	27	21
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	33	14	89	65	26	18	65	26	18
2	6	2	1	12	5	2	9	9	9
3	17	24	68	26	35	41	6	2	17
4	1	2	1	12	14	1	35	19	30
5	17	18	55	17	36	43	33	48	43
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	40	24	32	25	12	6	2	1	7
2	7	4	0	3	4	0	1	1	0
3	11	17	63	10	22	54	1	0	0
4	11	19	27	8	0	0	16	5	7
5	39	34	28	6	11	16	2	0	0

TABLE 12: Behavioural response to 10 mg/kg 5-Methoxy,-N,N-demethyltryptamine i.p. (For mean response ± S.E.M. during each time interval see Table 13 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	39	43	155	54	80	126	31	36	35
2	56	35	115	64	35	128	54	59	27
3	27	29	101	3	9	89	25	22	157
4	49	7	99	56	20	25	45	19	15
5	20	26	152	46	17	9	49	26	15
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	24	38	29	17	50	103	5	9	39
2	28	60	91	26	32	67	27	29	46
3	67	20	44	79	34	17	56	46	36
4	39	32	31	24	9	19	25	18	16
5	11	16	20	3	4	4	5	5	5
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	0	0	21	11	20	35	0	0	5
2	7	5	9	28	31	73	5	0	0
3	7	16	18	8	6	0	3	1	0
4	2	3	4	0	0	0	7	1	0
5	13	6	0	3	2	4	19	8	7
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	1	2	23	24	41	59	15	28	42
2	11	4	1	24	20	50	5	1	6
3	6	0	0	1	1	0	24	10	0
4	0	0	0	9	3	3	0	0	0
5	9	4	2	2	0	0	14	6	9

TABLE 13: Effects of pretreatment with 25 mg/kg desmethylimipramine hydrochloride i.p. on the behavioural response to 1 ml/kg physiological saline. (For mean responses ± S.E.M. During the different time intervals see Table 15 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	9	28	24	6	1	5	5	0	0
2	4	24	64	5	20	7	12	39	8
3	9	48	32	1	5	2	0	14	4
4	18	39	22	12	4	10	8	6	4
5	9	35	77	4	20	9	11	3	0
6							4	8	4
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	4	0	3	2	0	0	7	6	8
2	10	33	19	14	30	15	3	11	15
3	0	0	0	2	2	0	4	13	4
4	9	3	4	8	6	8	4	7	5
5	8	21	10	13	14	15	9	9	8
6	9	15	13	2	2	1	8	14	9
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	0	0	3	3	1	0	1	6	5
2	7	1	33	0	0	0	3	0	18
3	1	1	0	4	0	1	2	0	0
4	9	8	8	21	5	3	12	5	7
5	6	8	4	3	3	6	2	5	3
6	3	1	2	3	2	0	4	0	0
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	0	0	0	2	1	0	0	0	0
2	3	5	7	8	8	2	5	11	16
3	4	15	7	1	1	29	9	1	0
4	10	0	0	4	7	7	6	0	78
5	1	1	1	5	5	2	1	7	8
6	9	0	0	5	4	0	9	22	18

TABLE 14: Effects of pretreatment with 25 mg/kg chlorimipramine hydrochloride on the behavioural response to 1 ml /kg physiological saline. (For mean responses ± S.E.M. during the different time intervals see Table 15 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	20	70	37	23	35	20	26	25	19
2	26	70	54	10	19	9	11	9	5
3	29	86	53	34	53	38	15	26	14
4	11	21	16	16	18	11	19	0	15
5	13	46	39	7	15	4	14	9	8
6	20	47	48	25	24	14	19	11	5
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	20	30	11	10	21	15	12	11	13
2	9	18	10	13	6	7	12	15	1
3	5	8	1	8	12	4	4	5	0
4	9	7	4	8	15	5	14	16	0
5	21	14	9	14	18	5	9	9	3
6	33	16	5	20	4	0	31	29	46
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	4	6	24	0	0	0	7	3	7
2	9	16	5	6	9	2	16	14	0
3	1	1	0	0	0	0	16	36	28
4	10	10	5	22	28	12	29	28	6
5	12	18	5	7	11	10	18	47	64
6	38	19	43	29	38	38	19	20	28
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	1	0	0	1	1	3	0	0	0
2	9	14	11	11	32	21	7	0	0
3	6	7	5	6	0	0	1	1	0
4	15	12	11	11	7	2	13	17	14
5	10	2	0	4	3	0	4	0	0
6	25	37	36	24	17	7	4	17	40

TABLE 15: Effects of pretreatment with 50 mg/kg "GEA 654" on the behavioural response to 1 ml/kg physiological saline. (For mean responses ± S.E.M. during the different time intervals see Table 15 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	18	65	72	17	51	35	19	50	29
2	3	5	11	3	12	15	8	16	20
3	38	84	41	42	65	29	30	22	14
4	17	70	49	15	44	31	13	21	10
5	20	54	23	32	26	19	19	31	23
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	36	43	17	21	37	75	22	51	47
2	0	6	0	1	4	22	8	15	24
3	17	25	16	26	38	116	22	22	15
4	27	29	6	19	25	10	24	58	32
5	37	39	17	30	26	34	24	28	11
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	10	4	20	14	35	15	23	42	21
2	2	9	20	9	8	21	10	16	33
3	23	25	20	13	14	5	3	0	0
4	18	41	36	24	53	35	18	37	19
5	25	22	3	49	20	3	61	38	16
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	9	3	0	4	1	0	4	0	0
2	0	4	0	17	30	26	7	12	11
3	11	23	27	37	52	56	29	15	6
4	21	43	22	27	33	24	19	31	10
5	24	19	8	24	23	8	33	9	0

TABLE 16: Behavioural response to 10 mg/kg "LRCL 5182" i.p. (For mean responses ± S.E.M. during each time interval see Table 17 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	5	48	65	11	20	26	11	4	22
2	16	69	43	13	70	56	12	71	46
3	11	91	102	10	42	85	23	47	57
4	10	35	23	18	24	43	20	24	10
5	29	67	32	16	56	23	24	97	26
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	0	1	0	0	0	5	6	17	38
2	18	78	161	11	94	71	16	85	65
3	26	48	43	56	58	52	34	68	47
4	36	36	18	48	31	9	49	39	12
5	41	103	43	22	128	52	38	122	56
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	25	40	33	15	37	28	22	38	37
2	35	130	75	31	108	134	57	133	55
3	21	83	80	30	77	80	53	79	21
4	26	39	15	29	31	12	28	50	39
5	33	124	45	37	139	30	56	113	20
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	22	40	11	46	36	10	22	48	23
2	55	117	49	44	122	76	43	103	48
3	49	89	25	56	84	26	51	94	49
4	23	50	26	20	51	42	17	54	44
5	37	124	29	31	99	20	40	120	41

TABLE 17: Behavioural response to 20 mg/kg "LRCL 5182" i.p. (For mean responses ± S.E.M. during each time interval see Table 17 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	18	69	65	41	74	51	33	113	136
2	83	61	67	21	58	85	86	99	50
3	404	178	62	465	20	6	424	22	8
4	23	105	248	54	116	35	43	136	75
5	11	36	27	21	35	10	47	51	14
6	21	111	92	93	119	54	149	109	58
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	73	104	118	47	91	259	27	72	357
2	86	48	31	107	97	46	23	69	48
3	258	42	15	170	47	41	39	61	83
4	46	162	99	117	159	104	133	138	102
5	88	110	17	79	90	26	46	53	32
6	201	107	91	89	172	119	58	111	291
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	25	54	128	60	52	119	31	35	130
2	66	62	82	59	53	60	75	36	156
3	4	18	177	0	5	118	2	14	144
4	164	94	36	292	36	5	278	29	5
5	25	56	18	39	52	91	33	52	141
6	19	37	350	63	21	260	188	34	182
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	35	27	110	19	15	36	22	37	161
2	64	19	89	115	21	44	129	33	179
3	1	6	212	0	2	158	19	17	135
4	233	32	86	232	2	0	213	8	7
5	35	46	46	24	42	24	27	24	34
6	75	21	384	96	19	261	53	3	306

TABLE 18: Behavioural response to 2.5 Benztropine mesylate i.p. (For mean responses ± S.E.M. during each time interval see Table 17 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	37	118	114	28	136	44	79	89	35
2	19	90	93	25	60	73	23	23	49
3	49	87	78	61	102	62	67	40	30
4	29	118	63	66	78	43	60	32	17
5	9	57	88	35	56	59	55	32	30
6	29	120	92	61	93	72	79	53	45
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	43	58	19	57	67	23	57	60	55
2	10	12	168	19	15	88	13	11	51
3	52	33	-	29	21	11	15	25	10
4	68	14	9	61	12	14	73	40	28
5	58	27	-	50	10	25	14	2	7
6	87	44	52	106	25	18	114	13	24
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	17	10	48	34	26	43	49	23	213
2	21	14	38	12	16	29	23	8	11
3	43	12	11	41	21	12	36	31	24
4	30	25	79	64	31	25	25	16	19
5	22	12	-	21	12	21	16	5	25
6	107	16	40	85	18	19	67	24	14
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	46	18	13	28	19	15	42	29	14
2	26	13	22	3	1	0	1	0	8
3	26	37	-	20	46	37	13	16	16
4	47	29	19	35	15	9	48	53	34
5	28	9	59	11	8	17	23	3	-
6	65	10	162	62	40	82	56	12	46

TABLE 19: Behavioural response to 5.0 mg/kg benztropine mesylate i.p. (For mean responses ± S.E.M. during each time interval see Table 17 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	35	108	58	67	141	36	63	139	33
2	32	83	68	74	81	52	62	47	15
3	10	85	30	7	33	12	14	24	7
4	36	122	61	106	71	29	129	80	25
5	21	119	117	64	169	63	48	156	68
6	34	59	154	89	37	-	100	51	29
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	62	117	64	98	92	54	73	51	14
2	75	81	25	79	32	11	87	41	19
3	6	6	4	3	19	7	9	16	17
4	158	30	8	261	2	0	112	12	20
5	43	140	60	36	108	76	32	49	14
6	139	18	36	166	0	20	121	27	-
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	78	82	36	74	43	16	88	55	43
2	70	44	17	92	33	13	55	47	31
3	13	42	13	8	2	0	13	46	33
4	196	0	0	186	0	0	146	18	7
5	36	116	73	44	72	33	28	29	18
6	150	17	17	154	16	30	132	0	32
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	76	53	39	20	7	1	75	74	21
2	87	32	23	10	0	0	71	71	26
3	11	19	76	5	4	2	4	0	0
4	142	5	5	163	2	0	143	2	0
5	62	48	29	17	0	8	48	48	27
6	86	2	23	77	22	-	100	36	22

TABLE 20: Effects of pretreatment with 25 mg/kg desmethylimipramine hydrochloride i.p. on the behavioural response to 4 mg/kg dL-amphetamine sulphate. (For mean responses ± S.E.M. for each time interval see Table 19 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	43	85	56	121	74	48	281	39	42
2	16	21	51	14	12	27	37	20	10
3	9	3	8	29	1	0	135	9	0
4	8	43	15	28	41	5	175	20	0
5	30	40	27	19	36	18	135	7	74
6	3	5	-	40	38	58	10	41	134
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	154	29	28	239	9	4	284	0	0
2	34	19	32	45	7	0	101	2	23
3	166	2	0	157	2	8	151	0	0
4	136	6	86	248	10	0	147	12	0
5	168	1	31	158	0	0	207	0	0
6	67	129	130	109	159	104	104	140	36
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	218	0	0	211	0	0	86	0	0
2	186	0	48	143	0	72	88	0	0
3	196	0	0	109	2	7	180	2	0
4	105	0	0	61	6	0	66	0	0
5	63	0	0	27	2	0	3	0	0
6	186	71	7	217	53	0	260	24	5
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	143	0	0	86	37	0	87	31	2
2	70	0	9	18	0	0	21	0	0
3	274	0	0	201	2	2	107	0	0
4	29	0	0	68	1	0	17	0	0
5	10	0	0	3	0	0	1	0	0
6	332	21	0	329	4	0	377	0	0

TABLE 21: Effects of pretreatment with 25 mg/kg chlorimipramine hydrochloride i.p. on the behavioural response to 4 mg/kg DL-amphetamine sulphate. (For mean responses ± S.E.M. for each time interval see Table 19 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	20	91	46	11	60	37	18	57	37
2	9	74	173	11	86	39	13	109	46
3	4	27	29	14	78	59	35	51	22
4	16	57	25	46	32	23	108	87	46
5	11	63	95	40	52	20	118	77	221
6	42	73	60	12	31	33	60	67	79
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	33	60	55	80	105	19	175	104	12
2	20	152	137	22	150	183	16	195	38
3	53	86	19	103	93	16	120	51	73
4	206	81	58	275	42	30	261	26	14
5	132	89	80	132	97	0	109	84	0
6	151	54	41	197	57	41	244	28	34
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	327	35	8	440	0	0	488	2	0
2	26	189	28	41	219	125	51	221	45
3	198	20	27	168	12	30	228	20	40
4	266	26	31	248	6	6	119	7	19
5	136	49	0	118	67	41	96	58	1
6	251	18	42	273	4	8	253	4	2
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	464	5	0	559	3	0	616	1	0
2	70	241	50	73	234	48	64	193	55
3	238	0	0	276	6	11	240	11	42
4	146	17	5	224	0	0	194	13	11
5	95	46	32	123	25	31	121	20	25
6	250	5	0	269	10	2	317	10	15

TABLE 22: Effects of pretreatment with 50 mg/kg "GEA 654" i.p. on the behavioural response to 4 mg/kg DL-amphetamine sulphate. (For mean responses ± S.E.M. for each time interval see Table 19 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	159	19	34	156	24	25	200	42	12
2	12	41	15	34	49	15	20	36	9
3	40	67	70	81	85	50	103	192	91
4	1	13	22	21	26	16	20	25	20
5	21	23	104	38	49	32	49	72	36
6	22	77	27	48	54	34	128	78	31
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	236	33	8	322	4	0	304	0	0
2	36	29	3	186	52	5	157	64	10
3	271	154	65	443	36	1	463	4	129
4	127	68	31	225	38	22	260	33	30
5	69	70	21	87	54	26	123	33	22
6	201	17	0	187	0	0	163	0	0
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	339	0	0	335	0	0	323	0	0
2	140	39	0	144	53	2	177	42	3
3	527	24	20	499	28	13	526	11	74
4	280	26	28	281	19	18	236	46	22
5	124	21	9	137	27	43	134	29	23
6	186	0	0	189	0	0	206	0	0
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	187	20	5	219	2	2	258	2	0
2	179	25	3	125	27	3	183	16	1
3	527	6	4	578	4	1	548	5	70
4	245	51	17	259	13	4	227	54	21
5	121	64	21	140	23	11	137	24	11
6	165	0	0	180	0	0	196	0	0

TABLE 23: Effects of pretreatment with 15 mg/kg "SKF-525A" i.p. on the behavioural response to 4 mg/kg DL-amphetamine sulphate. (For mean responses ± S.E.M. for each time interval see Table 19 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	4	30	43	25	40	28	77	42	8
2	43	86	40	29	102	45	22	86	27
3	9	45	11	8	20	6	0	0	0
4	7	79	23	19	73	18	52	98	44
5	39	65	49	14	9	0	61	0	-
6	18	61	85	23	102	130	15	103	124
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	124	26	19	103	22	12	125	18	11
2	19	111	14	31	60	18	48	44	11
3	7	0	0	6	13	23	9	44	14
4	118	69	28	115	53	35	145	53	26
5	172	0	-	242	15	58	329	2	0
6	41	141	114	94	101	115	187	37	122
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	107	20	16	70	21	17	60	23	28
2	45	41	9	69	30	11	30	64	15
3	11	30	22	12	29	33	27	47	20
4	138	35	17	140	39	10	125	55	20
5	386	0	41	203	26	44	197	56	50
6	234	6	47	217	0	0	178	0	0
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	52	26	19	101	30	21	105	14	6
2	23	43	17	18	45	18	22	17	12
3	40	53	36	71	61	30	84	67	22
4	105	47	10	108	54	10	62	75	38
5	179	80	42	96	62	91	102	64	56
6	202	0	0	85	0	0	68	0	0

TABLE 24: Effects of pretreatment with 30 mg/kg "SKF-525A" i.p. on the behavioural response to 4 mg/kg DL-amphetamine sulphate. (For mean responses ± S.E.M. for each time interval see Table 19 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	28	36	28	34	73	26	70	120	26
2	24	11	6	9	18	7	7	31	9
3	4	32	34	16	33	29	52	36	22
4	14	75	75	6	71	58	16	82	62
5	19	71	59	28	91	72	65	108	68
6	13	28	17	55	99	24	60	147	31
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	218	31	6	291	6	24	309	13	4
2	55	2	1	107	5	3	227	0	0
3	65	112	24	99	125	21	171	55	11
4	32	135	89	50	121	84	41	126	87
5	129	67	18	225	24	0	196	33	0
6	130	83	16	234	7	2	280	0	0
TIME INTERVAL (min)	60 - 70			70 - 80			80 - 90		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	423	6	0	453	0	0	459	0	0
2	271	2	0	348	2	0	421	2	0
3	187	31	0	130	42	6	44	21	14
4	56	85	47	46	115	40	51	118	39
5	281	36	0	342	2	0	251	4	0
6	294	0	0	320	0	0	384	0	0
TIME INTERVAL (min)	90 - 100			100 - 110			110 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	461	1	0	439	2	0	388	0	0
2	441	0	0	452	0	0	437	0	0
3	152	4	4	122	9	3	156	20	6
4	42	118	88	65	141	112	54	117	94
5	210	13	29	164	3	8	129	12	38
6	422	0	0	425	0	0	432	0	0

TABLE 25: Behavioural responses of animals with sham lesions of the caudate nuclei and accumbens nuclei following administration of 1 ml/kg physiological saline i.p. (For main responses ± S.E.M. see Table 29 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	34	69	44	27	63	82	22	38	8
2	37	58	120	18	19	20	39	19	4
3	26	57	50	15	15	9	15	20	36
4	22	54	48	26	29	18	18	44	33
5	22	82	88	43	70	54	24	53	47
6	13	65	70	26	38	66	16	30	66
7	35	91	116	21	48	74	22	25	42
8	28	84	100	22	63	85	26	82	86
9	RECORD MISSING								
10	22	67	73	25	37	32	28	27	32
11	20	83	91	9	53	49	34	57	30
12	22	72	114	27	45	16	28	37	22
13	17	79	75	27	75	81	25	64	62
14	9	59	72	12	26	35	15	10	12
15	16	67	81	17	43	60	31	40	28

TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	27	51	46	23	46	22	32	50	22
2	35	24	16	25	23	14	16	16	6
3	7	18	52	16	11	28	1	1	0
4	13	31	57	19	51	72	0	4	58
5	23	55	49	15	44	54	8	44	85
6	21	37	50	44	30	-	28	22	36
7	14	45	86	10	12	24	14	4	8
8	12	61	93	32	18	35	34	5	16
9	RECORD MISSING								
10	20	22	7	2	9	27	32	25	31
11	33	49	35	20	46	40	18	19	9
12	33	37	47	26	33	49	16	19	17
13	15	50	112	16	46	53	2	4	11
14	10	16	26	14	20	19	43	4	3
15	21	27	24	29	26	28	23	26	30

TABLE 26: Behavioural responses of animals with 6-hydroxydopamine (6OHDA)-induced lesions of the accumbens nuclei following administration of 1 ml/kg physiological saline i.p. (For mean responses ± S.E.M. see Table 29 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	52	54	24	35	25	10	41	23	9
2	15	46	23	8	13	13	5	6	3
3	20	61	61	21	27	20	21	11	7
4	17	58	85	8	5	8	34	24	23
5	24	77	57	22	48	42	15	21	7
6	17	43	44	22	14	19	36	14	3
7	14	54	76	25	36	24	12	25	45
8	28	46	35	37	42	53	23	23	37
9	24	71	117	23	52	65	28	3	5
10	19	52	58	29	23	22	19	18	19
11	18	41	72	22	22	15	20	16	37
12	17	41	42	16	15	29	12	5	6
13	20	52	93	12	29	27	21	14	4
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	47	20	14	45	20	13	48	25	15
2	9	11	21	6	11	6	3	3	7
3	8	12	9	10	7	6	13	8	9
4	20	11	4	31	16	12	22	10	6
5	15	21	-	18	14	12	24	20	10
6	22	13	8	15	12	5	17	11	16
7	25	13	26	21	16	28	17	23	18
8	34	16	22	42	11	18	34	9	36
9	34	11	22	29	13	25	42	9	28
10	21	12	8	24	12	18	29	13	19
11	21	13	43	34	11	69	13	21	17
12	11	12	24	8	2	21	17	4	24
13	10	11	3	12	17	27	11	6	0

TABLE 27: Behavioural responses of animals with 6-OHDA-induced lesions of the caudate putamen nuclei following administration of 1 ml/kg physiological saline i.p. (For mean responses ± S.E.M. see Table 29 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	7	44	45	5	6	6	16	14	8
2	4	29	36	1	6	23	2	10	11
3	20	22	57	12	5	10	22	5	3
4	5	36	98	4	10	52	12	0	8
5	8	15	33	18	23	39	1	3	19
6	28	44	27	26	18	119	22	14	34
7	11	19	69	4	8	21	0	5	10
8	14	14	29	11	6	11	5	9	20
9	16	19	86	13	12	35	2	7	24
10	7	21	65	0	2	29	1	2	0
11	0	7	29	9	4	16	0	3	10
12	3	6	25	0	5	11	2	1	3
13	16	24	63	5	1	0	26	4	1
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	23	11	1	12	14	3	6	26	43
2	8	4	4	2	2	5	4	5	6
3	32	1	2	24	6	12	17	10	0
4	8	7	25	6	6	29	14	3	4
5	16	10	28	23	31	11	19	8	4
6	15	16	20	28	9	75	28	16	13
7	0	3	12	6	4	19	4	3	19
8	6	2	15	14	4	16	0	0	0
9	7	4	16	8	9	31	8	3	4
10	0	5	2	1	3	2	12	1	0
11	5	6	18	3	1	0	3	5	17
12	4	13	6	3	4	4	6	9	7
13	37	6	14	26	0	37	13	7	4

TABLE 28: Behavioural responses of animals with sham lesions of the accumbens and caudate putamen nuclei following administration of 4 mg/kg DL-amphetamine sulphate i.p. (For mean responses ± S.E.M. see Table 30 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	15	79	80	28	112	50	83	145	124
2	60	50	23	48	132	60	43	100	83
3	35	48	28	80	69	35	131	112	29
4	13	85	53	40	111	51	32	134	46
5	13	77	86	21	86	100	28	72	131
6	7	44	70	17	62	91	8	26	40
7	10	97	121	11	167	136	56	122	171
8	55	20	102	58	43	53	207	39	21
9	30	89	26	36	102	18	73	75	5
10	14	44	47	24	86	56	44	103	79
11	10	25	13	30	58	41	57	152	114
12	14	109	63	27	100	44	21	97	85
13	3	97	67	12	105	85	6	136	151
14	11	68	99	7	40	91	65	68	90
15	13	71	67	19	43	62	33	45	51
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	128	74	57	195	0	0	309	0	0
2	19	84	157	54	75	158	36	59	152
3	186	111	61	186	112	32	210	128	39
4	42	246	98	107	202	115	152	196	88
5	48	122	157	75	150	144	108	138	145
6	18	28	85	35	58	39	28	71	96
7	159	93	120	210	82	53	260	65	87
8	247	23	5	224	31	8	240	30	10
9	154	23	16	223	10	0	167	35	0
10	27	115	152	78	88	127	54	99	166
11	86	193	59	53	258	71	80	201	96
12	46	142	88	37	149	91	48	167	101
13	6	162	112	7	185	126	6	200	129
14	109	93	115	83	112	123	112	137	127
15	26	46	41	35	55	57	30	45	47

TABLE 29: Behavioural responses of animals with 6-OHDA-induced lesions of the accumbens nuclei following administration of 4 mg/kg DL-amphetamine sulphate i.p. (For mean responses ± S.E.M. see Table 30 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	28	45	28	53	38	11	84	22	9
2	19	53	42	71	42	21	71	42	21
3	24	27	15	73	18	0	96	3	0
4	5	12	38	7	17	64	76	62	40
5	14	53	84	20	45	91	24	86	75
6	19	56	41	21	29	24	89	34	20
7	28	43	48	43	65	44	104	68	36
8	41	37	38	111	18	18	141	23	23
9	19	58	74	28	61	70	50	59	49
10	55	48	26	81	12	1	98	13	38
11	35	62	61	185	20	21	151	62	2
12	24	35	28	72	5	15	90	4	4
13	40	21	18	56	16	17	75	16	7
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	80	15	9	67	15	25	77	15	12
2	119	26	7	96	34	16	115	21	55
3	164	2	0	158	2	0	152	0	0
4	93	45	41	73	34	34	53	18	28
5	73	100	120	43	115	126	141	90	92
6	90	58	14	76	57	41	53	76	30
7	114	50	21	118	76	32	155	51	43
8	129	23	45	150	20	31	131	14	16
9	83	73	24	87	46	7	82	36	87
10	116	4	0	126	0	0	106	9	8
11	110	145	84	184	63	54	243	16	85
12	57	20	13	80	15	28	77	9	4
13	113	5	2	150	0	0	131	1	0

TABLE 30: Behavioural responses of animals with 6-OHDA-induced lesions of the caudate-putamen nuclei following administration of 4 mg/kg DL-amphetamine sulphate i.p. (For mean responses ± S.E.M. see Table 30 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	3	33	30	12	33	30	5	50	35
2	1	5	100	5	9	135	6	8	134
3	16	45	78	29	36	78	22	35	91
4	9	24	112	7	42	125	9	35	105
5	18	28	63	9	66	94	19	52	61
6	9	36	56	12	56	74	17	58	69
7	7	16	40	18	37	70	70	64	98
8	20	65	102	17	64	83	19	42	103
9	7	13	54	0	4	81	1	3	67
10	3	11	27	4	11	55	12	23	58
11	1	1	8	0	0	0	0	1	5
12	18	11	20	8	13	101	0	10	178
13	2	8	30	0	0	0	1	2	0
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	8	59	32	10	57	37	19	38	16
2	4	4	99	4	3	68	8	5	52
3	15	34	55	15	39	55	17	25	38
4	9	42	116	12	35	122	9	28	82
5	28	45	56	27	54	57	15	44	103
6	25	70	71	20	62	79	21	70	50
7	102	77	198	130	80	106	141	86	115
8	15	54	121	19	42	39	13	52	64
9	0	0	45	0	0	64	0	0	44
10	14	24	66	18	28	70	15	19	60
11	0	0	0	2	1	10	0	5	12
12	2	10	300	1	7	363	4	14	389
13	0	0	0	0	1	5	0	1	4

TABLE 31: Behavioural responses of animals with sham lesions of the caudate-putamen nuclei or accumbens nuclei following administration of 16 mg/kg DL-amphetamine sulphate i.p. (For mean responses ± S.E.M. see Table 31 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	166	64	45	211	85	0	266	91	0
2	158	41	-	312	40	-	330	34	-
3	147	57	7	531	0	0	584	0	0
4	109	71	21	529	0	0	400	0	0
5	215	47	26	400	2	2	470	30	1
6	46	83	68	182	101	97	242	6	37
7	137	45	168	567	0	0	514	0	0
8	56	63	73	636	0	0	579	0	0
9	40	14	14	173	0	20	210	2	9
10	-	-	-	-	-	-	-	-	-
11	110	147	52	210	0	0	145	65	0
12	25	77	49	198	183	86	289	163	75
13	15	122	90	460	48	16	327	32	21
14	103	41	65	624	0	22	663	0	0
15	198	31	26	679	0	0	361	2	0
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	202	33	0	52	0	0	0	0	0
2	301	17	-	150	22	-	18	6	-
3	324	0	0	123	0	0	15	0	0
4	111	0	0	183	0	0	318	0	0
5	282	16	10	352	49	33	339	46	46
6	4	1	0	11	2	8	2	2	5
7	308	0	0	578	0	0	169	0	0
8	599	0	0	349	0	0	1	0	0
9	169	0	0	115	0	0	188	3	0
10	- -	-	-	-	-	-	-	-	-
11	52	32	0	72	16	0	4	2	83
12	490	72	32	261	4	21	220	0	0
13	157	44	35	229	35	17	239	6	3
14	587	0	0	354	0	0	34	2	0
15	378	0	0	304	0	0	38	0	0

TABLE 32: Behavioural responses of animals with 6-OHDA-induced lesions of the accumbens nuclei following administration of 16 mg/kg DL-amphetamine sulphate i.p. (For mean responses ± S.E.M. see Table 31 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	76	83	54	479	15	14	102	9	11
2	132	42	67	275	6	3	361	1	0
3	150	12	20	368	0	0	183	0	0
4	60	57	103	51	3	3	0	0	3
5	273	89	111	492	0	0	531	0	0
6	50	93	58	78	51	21	162	19	0
7	176	60	73	229	2	0	78	29	0
8	108	40	34	365	0	0	229	1	10
9	73	66	65	121	95	72	236	50	34
10	130	59	7	348	4	0	303	0	0
11	154	36	48	286	0	0	385	0	0
12	320	12	28	345	0	0	40	0	0
13	184	38	35	267	19	21	329	9	6
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	178	41	16	321	35	18	20	4	6
2	304	0	0	291	0	0	156	0	0
3	81	0	0	33	0	0	2	0	0
4	20	1	0	168	1	0	109	0	0
5	55	0	0	5	0	0	4	0	0
6	293	0	0	271	4	0	226	14	9
7	197	2	0	331	0	0	52	0	0
8	80	0	0	144	0	0	57	0	0
9	317	9	19	228	8	21	230	1	0
10	115	0	0	4	0	0	0	0	0
11	478	0	0	493	0	0	494	0	0
12	0	0	0	0	0	0	0	0	0
13	174	1	0	183	0	0	84	0	0

TABLE 33: Behavioural responses of animals with 6-OHDA - induced lesions of the caudate-putamen nuclei following administration of 16 mg/kg DL-amphetamine sulphate i.p. (For mean responses ± S.E.M. see Table 31 in main text.)

TIME INTERVAL (min)	0 - 10			10 - 20			20 - 30		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	24	61	83	22	102	182	31	113	183
2	0	9	84	0	5	202	6	2	205
3	9	40	-	13	59	106	7	81	39
4	7	59	120	3	52	149	3	44	151
5	85	80	79	75	63	48	26	136	38
6	26	64	122	39	62	81	19	31	4
7	7	27	34	91	27	17	56	23	0
8	12	29	32	36	9	17	22	31	17
9	19	58	50	18	90	50	9	16	10
10	25	27	31	30	33	39	37	37	58
11	0	0	0	1	2	1	6	2	8
12	0	4	339	0	0	267	1	6	308
13	1	3	13	4	1	0	5	0	0
TIME INTERVAL (min)	30 - 40			40 - 50			50 - 60		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC
1	21	121	196	18	156	206	11	113	190
2	4	10	143	2	8	87	0	3	79
3	5	68	38	11	77	33	7	55	4
4	6	36	171	4	49	177	8	43	184
5	41	136	70	31	109	82	33	110	114
6	35	7	22	56	0	4	30	0	58
7	99	20	0	92	27	0	145	6	0
8	73	14	26	34	18	6	8	6	8
9	3	12	0	7	17	9	17	32	12
10	37	32	42	41	36	19	65	13	80
11	11	5	12	8	4	0	3	0	0
12	3	11	336	1	5	352	4	8	384
13	2	2	1	4	0	8	0	0	2

TABLE 34: Behavioural responses of nialamide-pretreated rats following bilateral injection of 1 ul physiological saline into the accumbens nuclei. (For mean responses ± S.E.M. see Table 33 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	2	13	2	0	0	0	5	6	9	0	0	0
2	2	9	16	13	4	0	2	3	0	0	0	5
3	39	37	51	42	27	25	62	41	33	39	45	43
4	14	7	128	10	6	4	9	3	0	4	9	12
5	4	3	11	2	6	3	2	1	1	4	0	0
6	11	34	-	2	11	-	4	13	52	26	18	34
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	0	0	0	0	1	0	0	1	2	4	2	0
2	1	1	40	1	3	19	10	1	0	29	26	36
3	27	15	29	8	3	28	20	10	28	24	7	33
4	18	4	0	5	2	0	17	5	0	0	0	0
5	5	2	16	15	1	5	3	5	4	4	0	0
6	27	32	68	44	34	53	36	28	-	38	34	50
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	12	7	4	6	9	2	8	10	3	16	15	5
2	0	1	1	0	1	1	28	26	68	3	7	11
3	17	15	12	64	6	10	21	10	3	39	30	6
4	6	7	0	3	5	0	0	0	0	10	11	13
5	6	1	0	5	2	50	25	0	0	24	0	0
6	82	36	24	74	35	91	61	16	29	47	7	59
TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	40	2	2	63	26	9	27	3	0	2	3	12
2	5	1	0	46	31	49	17	21	32	23	14	9
3	19	7	23	38	6	0	83	25	22	75	48	67
4	2	3	5	12	10	40	24	34	15	16	23	12
5	27	17	13	16	6	0	11	18	3	52	9	5
6	39	37	101	101	30	87	55	11	56	59	17	-

TABLE 34; continued

TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	110	24	51	38	5	0	51	27	15	14	0	1
2	56	25	27	3	0	77	10	9	5	82	51	15
3	78	54	45	36	6	36	16	3	11	47	52	80
4	0	1	0	37	55	28	11	17	14	22	2	63
5	65	8	4	42	13	3	41	6	6	41	1	0
6	18	5	5	27	17	44	6	1	8	0	0	-

TABLE 35: Behavioural responses of nialamide-pretreated rats following bilateral injections of 5 µg dopamine hydrochloride into the accumbens nuclei. (For mean responses ± S.E.M. see Table 33 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	30	50	77	31	21	87	80	122	101	211	329	144
2	22	17	33	7	30	38	26	71	75	17	351	290
3	40	29	23	9	20	26	33	227	255	48	421	432
4	11	26	19	24	93	51	29	187	106	39	237	206
5	19	59	60	63	90	135	16	22	22	15	32	31
6	2	12	43	19	52	49	26	106	61	71	165	124
7	3	8	5	2	9	8	7	21	47	20	99	92
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	139	374	244	262	147	229	126	128	279	79	96	237
2	23	663	416	15	896	387	16	1021	405	12	1051	471
3	21	545	662	16	559	884	23	453	717	51	247	234
4	90	271	159	124	235	89	150	233	52	109	214	71
5	34	30	10	17	12	22	38	13	28	55	15	27
6	45	120	99	27	66	51	3	13	5	3	10	12
7	32	355	520	11	78	75	1	2	1	12	7	3
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	99	187	178	97	261	263	124	265	229	79	186	248
2	16	1106	591	24	978	490	63	598	204	36	149	114
3	24	67	48	37	60	84	9	3	1	31	35	29
4	178	203	87	114	254	191	111	195	126	130	261	113
5	17	12	71	53	32	80	28	29	104	89	25	87
6	0	0	0	1	3	1	11	21	17	1	0	17
7	11	19	12	15	9	43	30	16	48	25	18	32

TABLE 35: continued

TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	39	103	200	109	127	220	91	71	181	125	56	156
2	39	131	102	15	23	111	15	22	4	8	3	11
3	67	23	31	17	6	40	65	1	14	22	3	16
4	59	84	14	19	36	33	3	1	3	1	0	0
5	44	36	77	31	26	13	69	29	19	45	19	21
6	10	9	22	22	10	73	19	24	21	14	27	33
7	2	8	8	18	11	15	6	14	44	15	6	18
TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	139	96	84	132	44	57	202	52	29	85	12	13
2	19	12	4	12	46	47	13	4	12	6	11	13
3	40	25	54	44	16	10	1	1	3	30	18	46
4	2	0	0	17	15	10	6	12	9	4	1	20
5	102	58	74	12	7	7	7	1	9	44	4	26
6	0	0	7	9	19	49	1	1	21	21	27	51
7	1	1	0	3	6	5	9	14	55	2	10	28

TABLE 36: Behavioural responses of nialamide-pretreated rats following bilateral injection of 12.5 µg dopamine hydrochloride into the accumbens nuclei. (For mean responses ± S.E.M. see Table 33 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	23	101	136	80	114	325	153	312	558	101	541	714
2	6	24	14	30	90	110	43	296	263	59	623	654
3	2	8	13	4	22	20	9	61	91	13	43	97
4	15	103	191	13	49	111	22	136	211	43	444	507
5	21	71	72	47	121	70	40	282	176	39	415	283
6	24	35	48	4	2	11	0	0	1	36	85	67
7	7	22	22	25	65	47	87	268	156	90	475	284
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	56	453	882	36	482	1101	38	439	1116	31	354	1205
2	81	643	929	74	755	1195	78	704	1155	116	736	1210
3	28	121	628	27	253	329	82	461	524	123	545	727
4	52	635	742	27	613	890	19	574	986	20	394	1001
5	60	524	387	89	713	514	57	778	573	56	731	776
6	105	192	223	109	269	436	95	172	277	71	174	343
7	144	5[illegible]	378	100	468	416	95	473	480	53	534	465
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	40	411	971	40	357	882	56	369	799	74	335	825
2	80	816	1054	43	742	1006	50	782	732	25	187	168
3	70	607	740	94	635	737	104	531	517	83	364	349
4	16	350	758	10	56	262	0	0	42	7	10	133
5	80	768	741	71	659	767	56	509	435	82	266	307
6	40	80	162	32	25	112	27	29	113	5	9	51
7	40	435	432	28	232	229	42	109	164	2	8	16

TABLE 36: continued

TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	58	322	676	48	296	561	39	215	572	30	247	562
2	109	167	122	51	13	254	19	8	181	46	58	80
3	18	21	87	8	9	96	10	11	150	11	17	117
4	0	1	21	0	0	3	1	3	8	5	1	3
5	37	87	145	42	67	127	16	24	97	24	23	70
6	33	28	86	28	28	111	56	25	146	91	55	113
7	34	65	77	9	5	23	14	27	46	15	28	50
TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	55	258	392	68	200	617	72	191	425	97	117	205
2	32	17	41	52	31	25	28	8	32	0	0	0
3	4	11	72	14	48	112	3	1	6	0	0	0
4	5	2	0	9	10	70	2	2	29	0	0	0
5	35	31	47	84	37	89	42	4	16	21	0	0
6	38	29	93	29	33	124	13	46	103	4	11	13
7	46	38	126	49	41	54	9	1	1	60	57	45

TABLE 37: Behavioural responses of nialamide-pretreated rats following bilateral injection of 25 µg dopamine hydrochloride into the accumbens nuclei. (For mean responses ± S.E.M. see Table 33 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	6	42	19	5	39	20	14	59	25	28	128	152
2	0	0	10	9	27	9	30	97	34	26	107	18
3	37	71	21	8	55	9	39	232	7	33	381	95
4	14	47	82	22	103	92	51	244	189	84	360	288
5	0	0	-	20	67	43	42	242	130	58	549	264
6	10	4	14	54	77	220	73	178	0	84	280	18
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	53	261	400	72	361	446	52	296	298	44	246	556
2	34	427	100	15	464	162	10	373	108	14	437	175
3	21	398	156	21	507	190	39	540	167	29	561	124
4	85	494	453	71	481	557	55	524	716	77	530	734
5	38	779	392	34	674	427	20	809	489	29	704	-
6	39	609	174	28	733	268	27	735	259	25	767	298
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	70	330	281	69	269	323	73	285	312	80	260	391
2	15	511	180	16	295	120	19	84	20	7	16	40
3	25	450	61	23	244	25	33	61	14	30	66	2
4	67	469	859	40	462	888	34	492	885	46	511	873
5	18	663	577	18	742	722	18	291	381	24	126	179
6	25	736	337	43	720	352	56	729	429	76	791	390

TABLE 37: continued

TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	74	272	401	59	217	342	47	161	125	27	56	30
2	92	121	21	0	0	0	2	3	16	7	4	0
3	80	38	5	72	47	4	20	8	0	60	40	14
4	74	440	514	91	507	340	99	490	311	69	243	179
5	1	18	169	16	22	82	142	86	73	53	86	94
6	103	708	355	132	556	394	246	156	49	182	58	15
TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	14	21	46	22	31	50	1	0	0	4	10	22
2	15	18	10	2	10	16	2	2	0	5	3	4
3	45	26	14	26	16	2	32	4	1	20	0	54
4	27	138	266	8	3	61	7	24	81	10	19	39
5	77	38	-	85	44	93	36	12	14	3	0	1
6	106	13	10	108	6	5	126	6	0	135	0	0

TABLE 38: Behavioural responses of nialamide-pretreated rats following bilateral injection of 50 µg dopamine hydrochloride into the accumbens nuclei. (For mean responses ± S.E.M. see Table 33 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	37	50	55	61	412	159	29	670	684	29	711	459
2	5	6	11	46	153	99	38	217	148	60	416	245
3	16	26	29	12	94	289	22	230	464	35	408	725
4	25	105	96	47	181	120	16	220	300	16	373	238
5	30	112	57	20	40	104	29	42	159	35	76	40
6	9	33	71	11	55	137	13	43	163	26	105	410
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	13	788	-	36	786	691	42	492	606	52	392	-
2	76	455	340	118	617	510	87	773	589	156	766	539
3	36	718	786	13	756	-	15	829	1012	19	627	1120
4	11	674	974	7	768	434	9	857	536	10	734	565
5	37	115	133	36	269	127	69	313	90	67	480	81
6	38	229	432	46	257	496	51	266	380	200	338	230
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	24	204	1002	40	287	755	60	407	608	113	568	619
2	213	881	538	204	795	661	258	700	710	236	669	615
3	28	253	1078	32	237	973	72	344	-	66	374	873
4	50	747	423	40	420	977	37	430	486	49	307	230
5	79	633	73	52	849	97	49	818	136	64	950	158
6	443	409	255	599	375	296	703	398	316	640	298	248

TABLE 38: continued

TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	138	411	567	171	488	-	178	511	548	81	343	484
2	239	404	404	255	272	227	287	196	217	80	51	120
3	70	525	664	99	469	501	121	200	180	99	150	-
4	7	17	101	28	51	49	8	45	64	1	2	36
5	88	666	133	94	676	121	113	500	126	57	232	134
6	786	345	274	783	352	182	524	222	225	393	282	248
TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	48	146	330	68	93	193	116	70	133	85	53	114
2	87	58	41	104	3	20	58	2	49	0	1	0
3	94	48	-	76	25	137	20	15	-	44	41	722
4	6	24	38	19	3	48	6	4	27	8	6	15
5	109	117	65	209	35	9	129	32	107	71	35	9
6	108	137	270	27	44	168	12	19	97	1	1	31

TABLE 39: Behavioural responses of nialamide-pretreated rats following bilateral injection of 1µl physiological saline into the caudate-putamen. (For mean responses ± S.E.M. see Table 35 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	5	26	39	10	9	0	17	20	5	4	14	3
2	9	18	21	32	16	0	29	0	0	28	10	0
3	3	18	69	0	0	0	10	0	0	14	3	23
4	9	23	-	42	12	2	32	13	15	31	3	2
5	8	33	37	9	25	2	32	33	104	17	29	11
6	33	84	62	67	48	27	56	26	5	32	17	33
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	10	9	4	10	4	6	18	17	41	40	33	15
2	82	0	0	26	0	0	17	0	0	19	0	0
3	7	0	0	56	0	0	7	2	0	10	4	0
4	107	22	15	41	26	31	30	0	1	66	2	2
5	19	15	36	0	1	10	8	8	11	14	11	2
6	76	13	26	55	12	31	8	2	0	95	56	108
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	21	12	8	36	18	3	27	16	2	1	0	0
2	18	0	0	79	2	0	185	0	0	90	5	0
3	5	3	1	21	0	2	44	19	0	45	24	1
4	32	0	0	88	2	3	64	19	41	40	10	32
5	31	15	10	41	37	33	30	20	38	32	39	26
6	39	18	27	16	21	37	0	0	0	9	17	16

TABLE 39: continued

TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	61	46	15	56	27	23	33	19	30	52	44	38
2	103	4	1	70	5	0	19	0	0	17	4	0
3	17	10	0	7	3	0	5	11	2	17	5	0
4	69	8	11	73	14	11	96	15	12	118	31	45
5	39	2	1	48	31	10	33	35	43	37	45	6
6	17	28	42	46	38	62	7	7	9	47	56	80
TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	47	27	59	58	18	32	15	13	27	22	7	2
2	1	0	0	2	0	0	0	2	0	6	0	0
3	11	5	0	28	10	0	60	12	1	27	4	0
4	111	27	65	76	26	87	66	38	29	56	36	39
5	28	41	15	60	16	8	5	4	12	3	0	9
6	49	34	72	60	50	97	18	28	34	2	6	8

TABLE 40: Behavioural responses of nialamide-pretreated rats following bilateral injection of 12.5 µg dopamine hydrochloride into the caudate-putamen. (For mean responses ± S.E.M. see Table 35 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	13	18	56	18	14	-	42	14	96	187	147	158
2	21	75	83	113	82	38	214	229	145	474	246	262
3	32	95	30	145	56	30	175	81	28	187	27	56
4	9	2	63	114	44		173	69	29	423	91	48
5	3	6	19	15	11	5	65	26	15	59	7	2
6	4	9	38	16	11	9	29	27	28	68	27	9
7	12	4	2	28	2	0	10	0	0	41	32	18
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	146	46	-	317	71	193	595	124	185	692	98	-
2	586	153	81	543	114	38	592	102	14	574	85	21
3	64	5	19	115	19	34	64	27	35	49	24	127
4	915	57	132	281	11	60	552	12	13	647	7	26
5	230	12	46	204	2	63	309	8	19	244	56	95
6	96	38	23	85	54	64	88	28	48	12	10	44
7	163	16	13	116	18	11	221	42	24	202	20	20
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	552	42	89	497	13	89	303	43	100	201	37	119
2	728	150	55	549	113	27	13	0	0	3	4	5
3	62	16	21	71	29	24	65	15	65	40	8	45
4	63	2	13	206	11	37	142	10	85	141	18	17
5	134	20	51	36	8	10	105	42	141	57	29	50
6	65	35	74	15	14	1	96	39	39	79	32	53
7	171	69	11	79	1	0	48	7	0	19	0	0

TABLE 40: continued

TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	133	0	7	120	33	37	64	53	90	58	51	47
2	108	13	8	10	0	0	50	10	47	27	3	8
3	40	6	28	62	11	23	33	19	56	61	19	40
4	82	0	0	59	17	15	22	16	25	21	14	15
5	65	36	52	47	41	103	54	27	41	54	36	87
6	25	12	12	46	35	38	21	18	42	37	28	29
7	71	18	16	11	3	0	49	31	10	45	14	11
TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	60	23	41	44	24	45	25	34	25	26	34	63
2	25	5	17	30	25	24	25	5	3	21	10	12
3	56	17	24	21	0	0	41	10	43	18	4	29
4	24	26	29	9	11	12	4	4	9	12	21	62
5	65	34	68	20	6	17	24	22	61	3	3	9
6	33	34	47	47	34	44	43	31	74	56	26	75
7	27	33	10	11	2	0	18	21	15	6	4	11

TABLE 41: Behavioural responses of nialamide-pretreated rats following bilateral injection of 25 µg dopamine hydrochloride into the caudate-putamen. (For mean responses ± S.E.M. see Table 35 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	9	13	50	19	29	9	74	104	15	117	346	22
2	45	119	81	182	80	83	168	108	109	320	153	146
3	14	23	10	32	43	19	122	106	32	400	120	75
4	36	37	29	113	56	54	171	83	65	225	114	108
5	38	31	45	233	34	9	215	139	20	206	162	30
6	60	125	91	145	132	82	492	63	64	556	111	109
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	76	463	11	91	427	50	186	432	142	213	428	163
2	202	200	160	118	162	208	115	196	245	353	223	192
3	298	434	175	490	338	263	1268	52	26	1438	15	8
4	316	155	129	311	126	156	340	96	190	321	107	31
5	202	133	19	271	147	21	264	167	123	530	97	88
6	574	70	90	834	59	74	1199	59	52	1090	86	66
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	219	371	160	259	322	101	387	369	156	581	348	144
2	399	194	207	461	158	180	220	116	177	652	38	100
3	1476	0	0	1756	88	11	1159	76	19	1156	76	5
4	364	122	144	337	158	144	450	70	124	467	29	61
5	525	102	75	684	92	59		62	54	752	111	67
6	1373	21	21	869	104	81	762	52	67	611	162	116

TABLE 41: continued

TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	313	201	74	484	123	31	508	119	55	432	185	71
2	790	28	61	421	94	98	173	62	118	116	22	23
3	1027	42	14	394	29	12	217	14	6	166	17	3
4	462	2	4	362	8	31	365	12	54	298	6	22
5	461	108	62	415	163	102	234	47	53	111	42	76
6	649	100	89	503	55	57	267	59	34	5	3	10
TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	496	68	29	296	49	61	358	40	18	111	52	100
2	54	20	15	24	5	6	110	41	53	3	6	6
3	105	18	8	82	24	48	53	14	2	43	18	12
4	204	38	35	212	8	46	243	21	15	235	2	0
5	47	10	53	0	0	1	72	60	84	23	6	53
6	78	24	41	168	60	50	79	47	70	101	21	33

TABLE 42: Behavioural responses of nialamide-pretreated rats following bilateral injection of 50 µg dopamine hydrochloride into the caudate-putamen. (For mean responses ± S.E.M. see Table 35 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	14	18	71	46	27	31	140	40	18	126	150	100
2	20	19	9	40	76	46	80	54	10	517	49	36
3	24	55	73	60	30	40	398	71	40	637	55	11
4	20	43	49	86	22	12	94	46	36	179	50	46
5	17	30	28	34	22	54	366	148	69	555	355	459
6	5	11	32	102	45	10	136	67	56	619	58	41
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	177	244	297	385	151	158	450	86	69	593	35	40
2	513	20	85	637	97	64	682	208	128	786	175	70
3	534	157	199	511	258	256	820	196	47	1174	99	86
4	786	8	0	638	74	22	695	39	77	820	5	1
5	532	423	547	656	426	344	521	598	581	807	570	527
6	848	104	26	716	71	29	861	16	7	968	128	3
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	611	59	81	637	35	45	574	93	173	732	130	128
2	764	181	-	1118	204	57	913	284	183	759	370	165
3	1422	18	19	1445	0	14	1043	0	0	924	2	15
4	645	20	23	766	42	23	973	33	7	705	82	67
5	786	611	453	725	357	721	596	318	280	944	192	63
6	1596	26	96	1760	21	69	1401	27	68	1570	30	30

TABLE 42: continued

TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	637	133	144	454	137	231	459	73	175	349	119	256
2	566	375	130	604	333	121	386	405	145	309	186	89
3	1592	18	92	1571	27	94	1651	0	0	858	46	93
4	590	81	66	564	176	106	562	117	57	547	227	79
5	824	108	68	676	135	155	504	105	171	126	55	131
6	1023	121	140	1203	71	120	626	77	146	310	48	172
TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	420	121	160	64	9	25	64	26	151	0	0	0
2	207	130	76	164	115	124	110	53	66	87	61	79
3	589	87	121	475	140	104	400	94	35	166	120	156
4	439	245	96	425	597	218	565	393	155	612	45	24
5	76	83	112	14	1	18	26	23	49	1	1	0
6	105	28	248	30	5	4	63	16	36	23	2	58

TABLE 43: Behavioural responses of nialamide-pretreated rats following bilateral injection of 50µg L-noradrenaline hydrochloride into the accumbens nuclei. (For mean responses ± S.E.M. see Table 39 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	38	93	112	36	65	61	85	57	94	45	60	84
2	17	32	-	9	16	42	29	21	51	26	27	37
3	20	67	121	17	67	76	25	73	158	20	98	107
4	8	23	20	4	12	11	4	8	17	3	6	0
5	11	29	28	2	6	18	5	4	19	2	3	5
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	34	40	119	31	87	129	17	71	127	9	76	134
2	11	32	92	26	27	46	8	25	-	26	25	21
3	26	103	185	11	98	180	14	59	137	14	35	107
4	4	1	13	1	0	0	1	0	3	3	4	5
5	2	6	3	8	3	1	0	1	2	9	0	0
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	6	36	12	5	35	24	3	42	22	5	16	12
2	16	2	48	10	9	17	12	9	3	4	7	10
3	10	35	103	9	12	52	0	11	13	6	18	27
4	2	0	22	14	17	11	8	4	0	2	10	2
5	0	0	13	23	17	40	16	2	6	2	1	0
TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	6	12	16	1	4	22	1	0	2	2	3	7
2	6	6	10	5	24	8	5	16	12	1	21	22
3	1	2	12	7	9	25	3	6	37	2	7	43
4	1	1	0	10	8	4	11	13	14	7	11	22
5	27	11	3	32	36	16	44	14	39	25	42	29

TABLE 43: continued

TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	1	1	9	0	3	4	1	1	0	6	3	0
2	4	16	1	5	7	8	6	7	7	11	13	21
3	1	6	10	0	5	6	1	10	11	5	4	4
4	16	20	34	15	18	28	6	23	30	2	4	7
5	11	12	6	14	15	23	2	3	9	2	3	8

TABLE 44: Behavioural responses of nialamide-pretreated rats following bilateral injection of 50 µg L-noradrenaline hydrochloride into the caudate-putamen. (For mean responses ± S.E.M. see Table 39 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	35	10	27	35	19	70	26	19	25	25	29	65
2	4	2	14	0	0	0	1	0	0	7	8	60
3	5	14	69	19	23	61	13	38	49	15	19	86
4	5	16	-	39	5	4	59	36	54	100	22	-
5	15	13	8	7	2	4	2	10	34	3	3	93
6	35	41	26	68	40	27	23	9	4	19	10	1
7	7	3	15	7	0	0	1	4	2	9	8	17
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	36	49	101	36	57	90	55	67	74	40	64	88
2	21	73	101	31	135	109	117	136	94	224	40	14
3	11	22	47	39	27	44	43	43	54	15	14	39
4	113	11	7	107	9	-	53	1	29	23	4	0
5	7	4	0	27	5	67	53	19	11	17	11	2
6	123	34	20	28	17	21	60	39	17	46	23	10
7	24	7	102	23	23	84	54	51	36	137	83	47
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	88	66	76	119	40	52	146	26	14	51	13	20
2	417	59	8	569	34	11	656	32	3	555	58	41
3	10	2	46	25	11	12	16	3	11	28	5	19
4	156	12	-	161	62	-	72	6	31	122	2	89
5	8	10	55	3	4	0	19	33	128	56	23	37
6	59	7	1	87	16	19	80	37	14	161	11	48
7	109	20	91	71	20	51	126	36	59	90	26	49

TABLE 44: continued

TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	11	4	8	30	0	30	63	11	132	101	33	14
2	714	57	21	646	29	18	702	0	23	539	62	66
3	14	4	19	37	17	66	49	8	20	74	54	52
4	170	2	77	136	58	53	254	10	73	292	32	50
5	110	34	104	342	107	92	188	64	31	23	0	0
6	175	13	35	48	3	16	98	19	30	64	13	17
7	129	57	60	129	48	103	121	77	114	135	43	86
TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	214	29	28	82	13	26	54	36	35	33	20	14
2	544	55	49	486	44	27	330	45	52	361	49	30
3	130	21	132	38	17	21	50	37	49	47	19	21
4	185	27	107	75	17	67	5	1	11	42	19	71
5	67	79	91	39	20	131	17	6	76	56	53	55
6	52	13	77	15	3	43	23	19	84	188	23	51
7	148	26	68	110	77	157	95	100	124	44	14	118

TABLE 45: Behavioural responses of nialamide-pretreated rats following bilateral injection of 50 µg 5-hydroxytryptamine bimaleinate into the accumbens nuclei. (For mean responses ± S.E.M. see Table 41 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	10	28	106	18	56	232	31	26	223	64	14	235
2	21	20	26	131	46	58	24	40	178	57	86	257
3	19	13	78	62	29	315	100	3	434	17	4	132
4	9	14	69	20	80	43	42	39	29	77	191	129
5	12	21	41	31	56	102	12	25	152	21	21	165
6	11	32	118	19	4	66	9	1	74	0	1	81
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	56	43	329	54	193	524	48	258	387	33	83	139
2	72	67	244	49	84	274	27	69	237	26	87	236
3	0	0	12	7	2	12	0	2	9	0	0	0
4	13	75	76	24	45	68	19	20	35	10	3	75
5	35	51	216	46	121	202	15	81	123	12	24	91
6	0	0	130	1	1	320	17	1	301	21	14	150
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	31	12	25	27	0	0	76	20	35	84	22	35
2	5	4	112	3	3	31	11	3	13	8	7	19
3	6	6	0	23	10	0	50	40	18	67	31	31
4	18	34	84	29	6	26	7	0	0	7	26	57
5	12	12	36	14	3	24	0	0	0	8	8	12
6	25	23	229	37	22	164	181	88	132	205	73	171

TABLE 45: continued

TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	10	1	18	50	18	95	24	26	15	13	1	16
2	39	25	63	13	14	38	29	26	19	23	19	36
3	46	57	103	10	5	16	16	28	28	18	8	23
4	27	33	14	48	6	18	72	25	18	71	14	15
5	21	16	32	14	15	28	9	3	18	24	2	4
6	33	30	-	41	74	125	12	1	12	0	0	0
TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	7	1	9	18	19	45	8	23	34	7	17	33
2	9	39	45	15	14	38	26	27	60	11	34	55
3	37	28	18	21	8	22	33	21	23	26	12	32
4	63	63	69	104	67	110	47	24	61	16	21	29
5	18	12	32	14	10	32	28	20	30	14	12	24
6	2	1	0	8	0	4	1	0	0	0	0	0

TABLE 46: Behavioural responses of nialamide-pretreated rats following bilateral injection of 50 µg 5-hydroxytryptamine bimaleinate into the caudate-putamen. (For mean responses ± S.E.M. see Table 41 in main text.)

TIME INTERVAL (min)	0 - 30			30 - 60			60 - 90			90 - 120		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	48	131	22	30	72	40	69	150	94	160	86	46
2	54	118	183	49	186	542	21	123	631	30	134	555
3	7	9	14	13	11	51	10	13	9	20	33	24
4	8	2	77	15	46	47	83	31	46	73	16	121
5	38	21	22	7	6	14	12	1	39	60	46	13
6	23	82	93	46	118	52	33	136	87	52	132	45
7	21	39	54	115	11	49	205	26	49	421	57	55
TIME INTERVAL (min)	120 - 150			150 - 180			180 - 210			210 - 240		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	97	65	60	118	76	67	198	155	125	164	85	70
2	27	140	662	18	148	578	33	180	515	38	143	401
3	16	46	38	12	31	27	51	41	43	10	18	32
4	57	18	122	72	13	74	27	9	44	61	3	146
5	83	41	1	131	74	9	120	51	18	122	68	56
6	54	53	23	56	83	128	32	42	74	33	9	17
7	412	40	67	421	59	33	281	29	23	143	41	14
TIME INTERVAL (min)	240 - 270			270 - 300			300 - 330			330 - 360		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	101	52	75	17	22	22	22	9	14	10	7	7
2	32	56	281	23	35	23	24	31	62	11	15	8
3	74	7	34	38	17	24	10	3	11	1	0	0
4	53	8	116	41	25	88	58	11	105	32	27	69
5	131	47	87	86	87	35	70	101	62	87	99	60
6	23	6	24	16	7	100	29	2	24	17	9	31
7	52	18	28	78	4	44	45	6	34	80	5	43

TABLE 46: continued

TIME INTERVAL (min)	360 - 390			390 - 420			420 - 450			450 - 480		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	21	34	40	15	16	14	37	43	44	23	26	69
2	15	44	38	28	19	26	18	13	39	13	9	12
3	1	0	11	2	0	0	0	1	70	3	3	2
4	32	17	58	34	0	8	56	30	31	29	10	65
5	101	92	70	61	138	115	120	57	77	113	72	44
6	28	15	25	43	17	21	38	15	25	43	31	54
7	67	2	3	58	18	10	81	3	26	71	15	62
TIME INTERVAL (min)	480 - 510			510 - 540			540 - 570			570 - 600		
RAT NO.	S	E	LOC	S	E	LOC	S	E	LOC	S	E	LOC
1	46	23	26	28	15	56	10	7	48	0	2	0
2	5	7	9	3	12	15	2	2	10	1	3	2
3	10	4	4	3	1	2	12	5	17	1	1	0
4	21	10	31	0	1	14	20	15	54	13	18	11
5	94	45	38	57	35	22	51	20	68	39	13	36
6	27	19	15	46	20	44	51	24	28	39	28	19
7	85	0	10	106	4	41	51	11	20	83	7	9